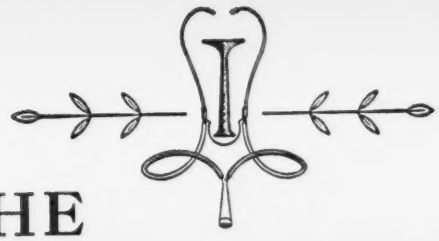

THE Journal of the Kansas Medical Society

MARCH
1957

VOL LVIII
NO III

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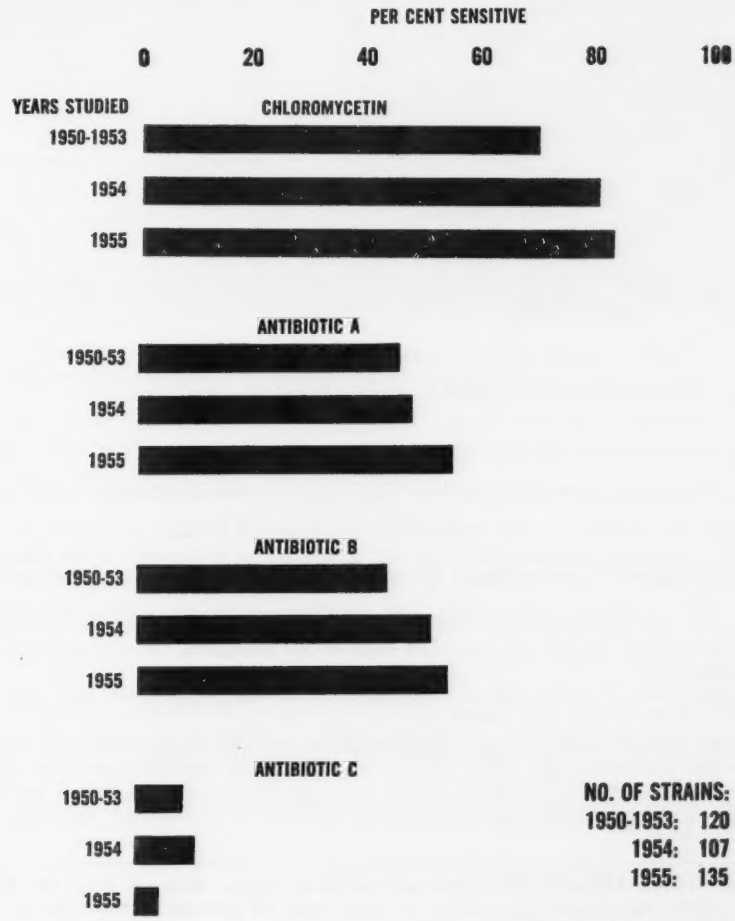

*This graph is adapted from a five-year study by Rantz and Rantz.[n]

THE JOURNAL
of the
KANSAS MEDICAL SOCIETY

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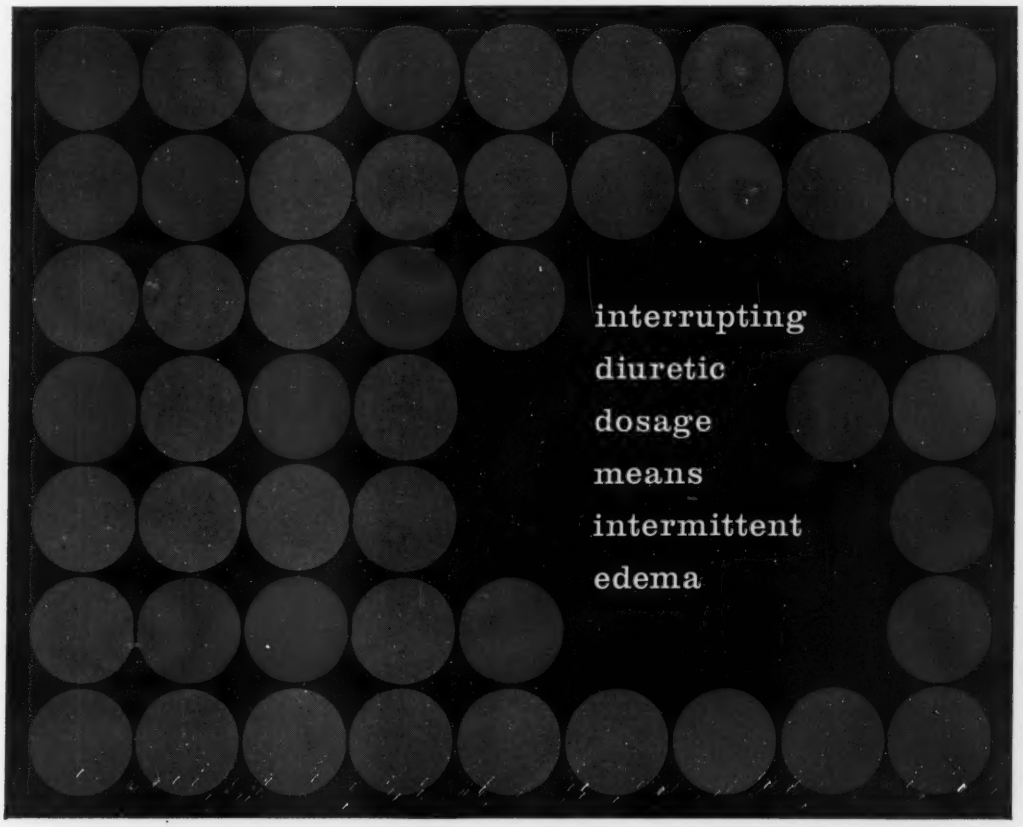

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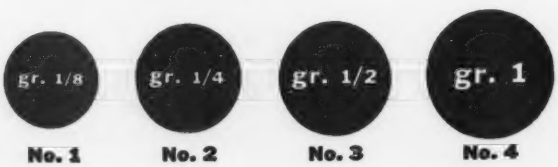

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1. Locket, S.: Brit. M.J. *1*:809 (Apr. 2) 1955.

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2. Wright, W.T., Jr., et al.: J. Kansas M. Soc. *57*:410 (July) 1956.

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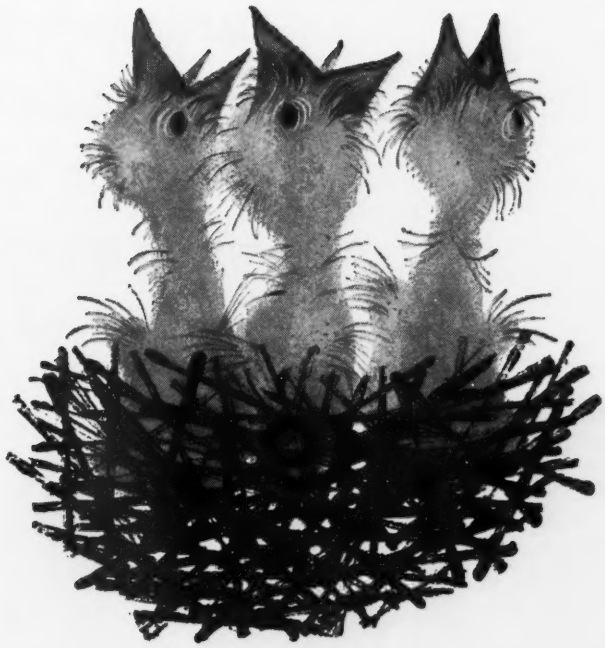

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1. Carter, C. H., and Maley, M. C.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 51. 2. Shalowitz, M., and Sarnoff, H. S.: Personal communication. 3. Shubin, M.: Personal communication. 4. La Caille, R. A., and Prigot, A.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 67. 5. Winton, S. S., and Cheserow, E.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 55. 6. Cornbleet, T.: Personal communication. 7. Loughlin, E. H.; Mullin, W. G.; Alcinder, L., and Joseph, A. A.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 63.

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*Geiger, E.: Digestion, Absorption and Metabolism of Protein, in Wohl, M. G., and Goodhart, R. S.: Modern Nutrition in Health and Disease, Philadelphia, Lea & Febiger, 1955, pp. 98-143.

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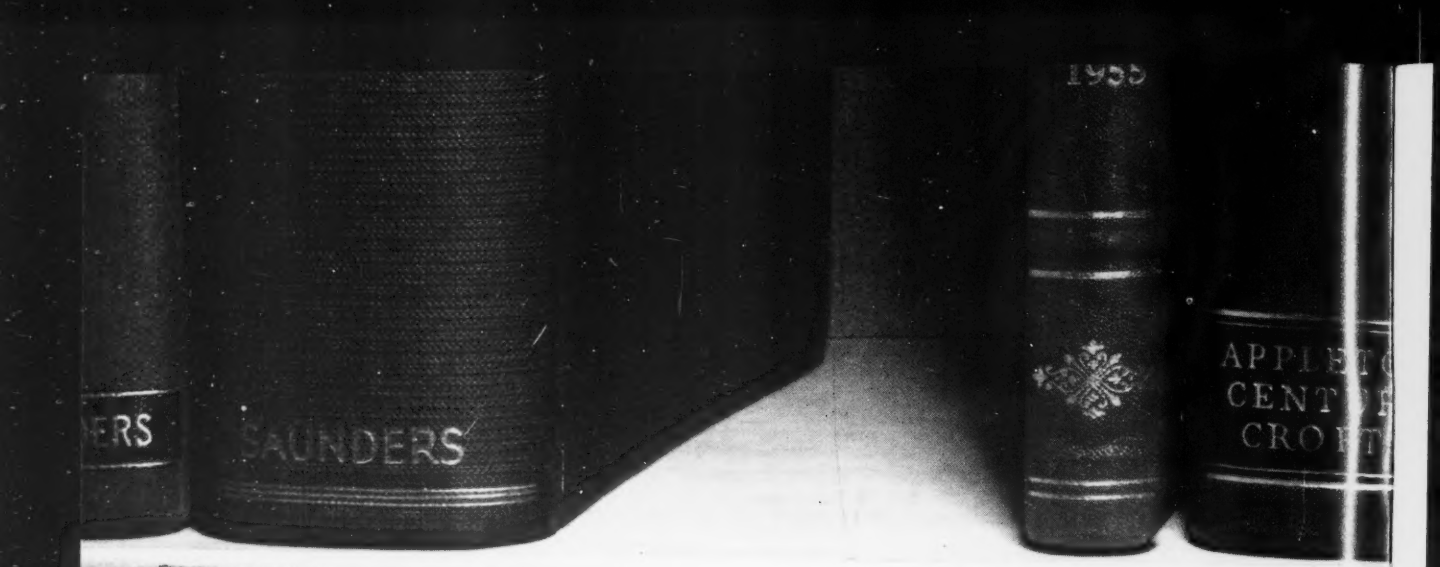

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A 24-year-old male, a chronic alcoholic, was admitted with a history of an alcoholic spree followed by a cough, greenish sputum and chills and fever.

Physical examination showed a temperature of 104 F. and indicated pneumonia in the right lower lobe. This was confirmed by X-ray. The sputum revealed gram-positive diplococci and blood culture subsequently grew Type VII pneumococci.

The patient was treated with erythromycin, 300 mg. every six hours per os. His temperature dropped to normal by 48 hours and X-ray of the chest revealed considerable clearing by the fourth hospital day. After 10 days hospitalization, the patient was fit for discharge.[1]

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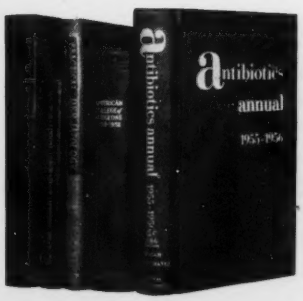

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2. Waddington, W. S., Maple, F. C., and Kirby, W. M. M., A.M.A. Archives of Internal Medicine, 1954, p. 556.

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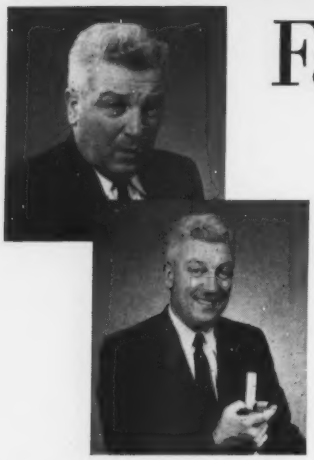

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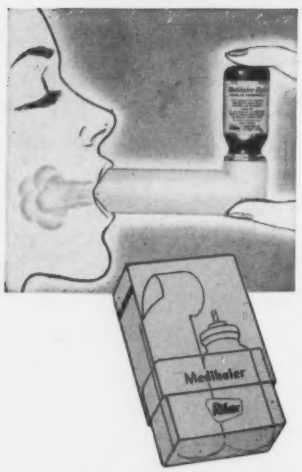

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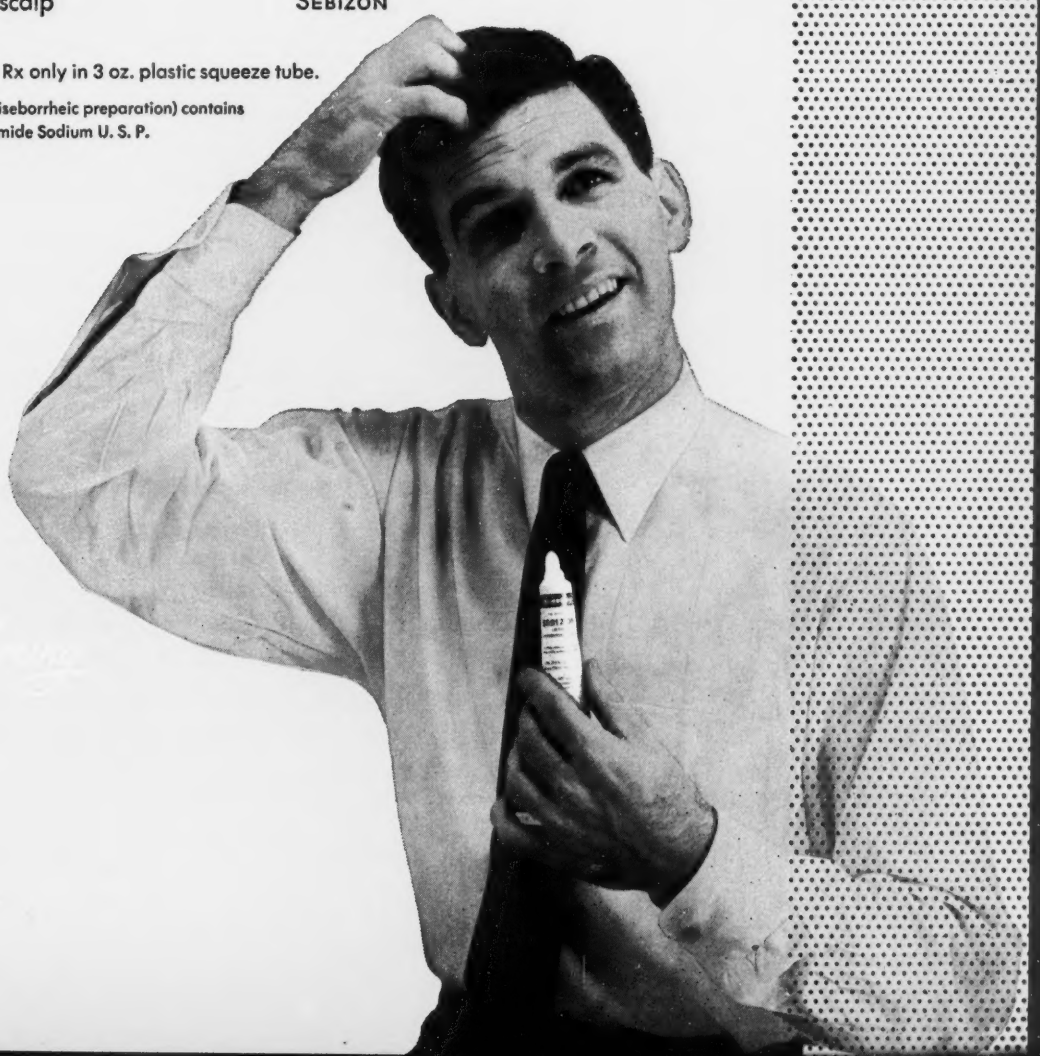

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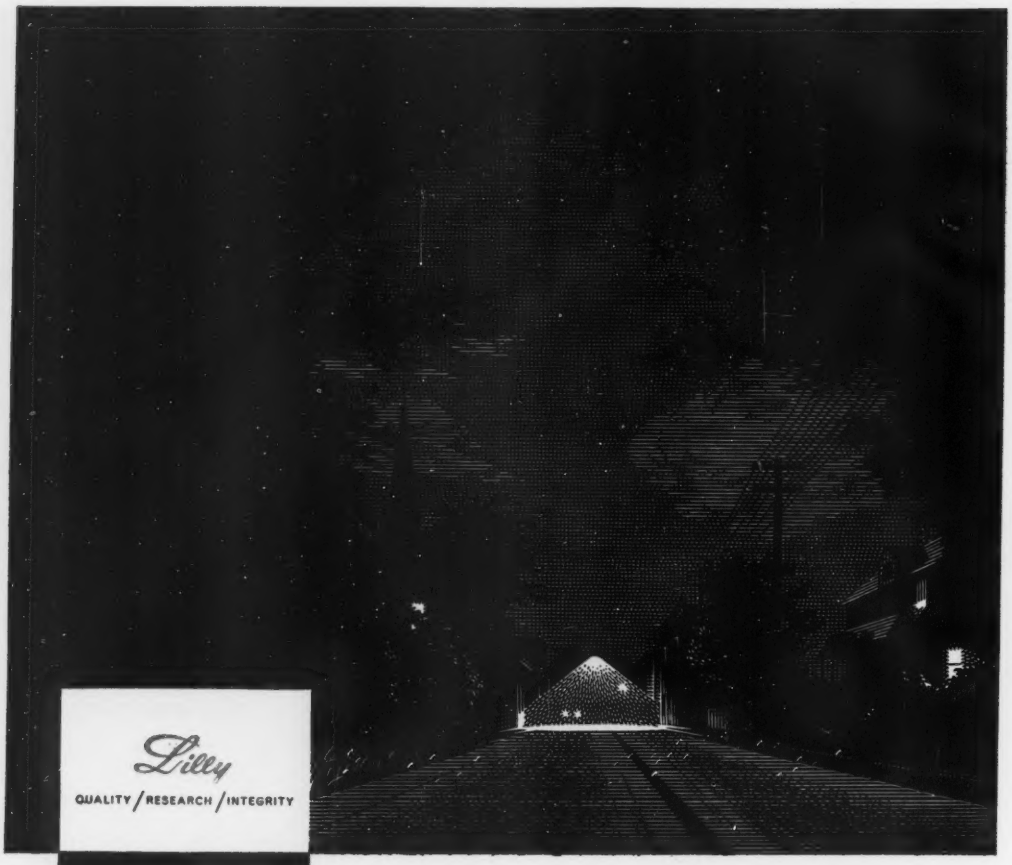

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The Medical Center Issue

An Introduction by the Dean

This is the fifth time that the opportunity has been presented to me to introduce the Medical Center issue of the JOURNAL. Retrospectively, it is pleasing to note that of the four basic needs of the Medical Center mentioned just four years ago, two have been met and one is now in the planning stage. Later in this issue you will read of our new library and its program, one of the two needs that have been met.

I have no desire to write at length in this issue, and I suspect that you would have no desire to read any lengthy comments that I might make. Our school's progress continues at a rapid pace and all of you, I know, are aware of it.

What I would like to say above all, and I do it now, is that I know of no medical school in this country that has the fine relationship with its state medical society that we do. I believe the Kansas Medical Society and the University of Kansas School of Medicine can take pardonable pride in this relationship; we might well point to it as an example that others can profitably follow. The knowledge that the school has the warm, generous, and complete cooperation of the Society makes my position an enviable one and my task an infinitely lighter one than it otherwise might be. For this cooperation I extend to all of you my own personal as well as my official thanks.

Until the annual meeting, where I hope to see all of you—my kindest regards.

W. CLARKE WESCOE, M.D.

Postgraduate Medical Education

Physical Facilities for Graduate Study at University of Kansas School of Medicine

Construction will begin this month on a one-story brick building adjoining Battenfeld Auditorium at the Continuation Center-Student Union Building on the University of Kansas Medical Center campus. This will provide permanent quarters for the administrative staff of the Department of Postgraduate Medical Education. It is expected that the building can be occupied in the fall of 1957. (See cut, Page 143.)

Physician enrollment in postgraduate education, both in-state and out-of-state, has shown a marked increase during the past three years, so additional office space for administration of the program is coming at a propitious time.

The new area will include a foyer, a combination secretarial office and registration counter, an office for the department chairman, as well as offices for the executive director and field representatives. Also included will be a conference room accommodating about 60, filling the frequent need for a moderate-size classroom for courses with limited enrollment or small group discussions. A mailing and supply room and a utility area for storing heavy auditorium equipment complete the space to be occupied.

The administrative staff of the department now numbers seven. Besides the chairman of the department and the executive director, there are three secretaries and two field representatives, and part-time clerical assistance. In the past it has not been possible to place the staff in one central location for the most effective coordination of activities. The new building will be a handsome addition to the campus group and a functionally useful one.

Postgraduate Medical Education

The Past, Present, and Future of the University of Kansas Program

MAHLON DELP, M.D., JESSE D. RISING, M.D., *and* WILLIAM D. NELLIGAN, B.S., *Kansas City*

History

With the exception of the years 1922 and 1926, the University of Kansas has offered some type of postgraduate instruction in medicine almost continuously for the past 45 years. Such instruction began in June of 1911 with a cooperative venture between the School of Medicine and the Kansas State Board of Health in arranging and presenting, on the Lawrence campus, the first annual five-day summer school for health officers and physicians. After the first three years, these courses were transferred to the School of Medicine at Kansas City and were expanded to two full weeks annually.

In 1927 the University Extension Division and the School of Medicine offered their first courses on the circuit plan, using six centers in the state of Kansas for the original trial. In 1928 five "short courses" were added to the activities and became permanent features.

In 1942 the president of the Kansas Medical Society requested the cooperation of the University of Kansas and the Kansas State Board of Health in providing intensive circuit-type courses for physicians of the state. Representatives of the three organizations were assembled as a joint advisory committee for the first planning session early in 1943. This union of energies has been continued to the present time.

The creation of the Department of Postgraduate Medical Education of the School of Medicine, in 1945, served to stimulate expansion of all postgraduate activities. This step represented the attainment of a degree of maturity in the administrative structure, permitting organized planning, unified administration, and development of policy based upon sound principles in medical education. Although chief responsibility for the entire program rests immediately upon the university and the medical school, the state medical society still retains co-sponsorship through its Committee on Postgraduate Medical Study.

The whole program of postgraduate medical education in Kansas is an integral part of the Kansas Plan for Rural Medical Care, formulated in 1948.

Presented by Dr. Delp, chairman of the Department of Postgraduate Medical Education, before the Congress on Medical Education and Licensure, Chicago, February 11, 1957.

This is the historical background for one program of postgraduate medical education, which may be considered a prototype of programs involving a medical school and a state medical society. The barest fundamentals involved in any educational project include a student, a teacher, and a curriculum; therefore, postgraduate medical education may be and is carried on in a successful manner using other methods. Several of such plans are being presented today.

Organization

The topmost administrative body of the University of Kansas is its Board of Regents, to whom the chancellor is directly responsible. He and the deans of the various schools formulate policy in an administrative pattern common to most state universities. The dean, with the aid of his faculty, guides activities and controls policy within the medical school. Postgraduate medical education is designated as a distinct function falling upon a separate department within the medical school. As such, it has its own responsibilities, prerogatives, and the usual amount of autonomy. Department administration is carried on by a chairman and an executive director.

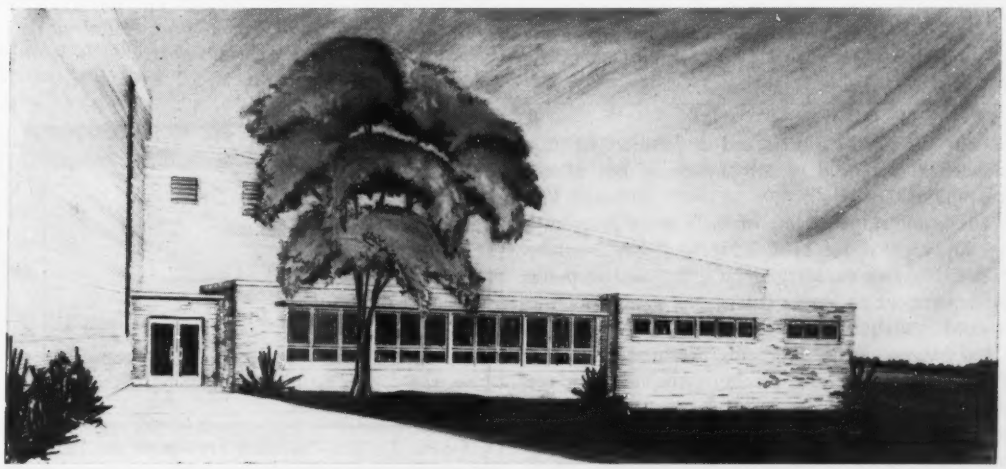
The Kansas Medical Society has an administrative structure similar to other such state organizations. Its committee for postgraduate activities is the Committee on Postgraduate Study. A joint advisory committee is composed of the group just mentioned, the chairman of the Committee on Medical Schools, the chairman and one member of the Committee on Rural Health, one official from the Kansas State Board of Health, one official from the Kansas Academy of General Practice, and additional selected individuals who join with the chairman of the Department of Postgraduate Medical Education and the dean of the medical school as an actual working and policy-making group. The term "working" is used advisedly, because this group annually spends from eight to ten hours in session discussing the past year's activities and problems facing the department, and actually building in outline the content and format of programs for the ensuing year.

It might seem that the organizational structure is too bulky and loosely-bound for good administration, but experience has proved this not so. The program administration, in the last analysis, falls directly and properly upon the medical school. The medical school also supplies the other essentials; i.e., (1) curriculum, (2) faculty, (3) facilities, (4) budget, (5) educational methods, and (6) evaluation of the enterprise.

Objectives and Purposes

The objectives of this program, as outlined in our last annual report, are—as might be expected—similar in general terms to all other such programs. Medicine has become so complex that it is obviously not possible to present a completely detailed and sustaining knowledge concerning every medical and related discipline in a four-year period. Consequently, four years of undergraduate medicine, internship, and even residency supply merely the foundation for a lifelong study of medicine. Continuation study, aimed at acquiring new knowledge and skills, renewing former ones, and preserving and increasing professional competence, constitutes postgraduate medical education. Providing environment and atmosphere for accomplishing this is the objective of the Kansas program.

Formerly designed for and directed at the generalists in our region, the program is now geared to the needs of every physician, regardless of his interest or field of specialization. Preservation of competence,



Architect's drawing of building to be completed next fall.

TABLE 1

COURSES IN POSTGRADUATE MEDICINE OFFERED BY THE UNIVERSITY OF KANSAS SCHOOL OF MEDICINE, 1956-57

FOR MEDICAL PROFESSION
Symposia (Short Courses)
Obstetrics
Internal Medicine
Pulmonary Disease Clinic
Gastroenterology
Surgery
Radiology and Radioactive Isotopes
The Heart: Cardiac Arrhythmias
Neurology
Symposium on Pain
Pediatrics
Electrocardiography
Hematology
Ophthalmology and Otolaryngology
Anesthesiology
Cardiac Auscultation
Symposium on Leptospirosis
Intermittent Courses
General Practice
Surgery-Operative Clinics
Kansas Circuit Course
Correspondence Courses
Interpretation of Electrocardiograms—Courses I and II
Special Skills Courses
Radiological Physics
Histochemistry
Clinical Use of Radioactive Isotopes
For Allied Professions
Operating Room Nurses Institute
School Health Conference
Medical Technology
Nursing and Nursing Education
Hearing and Speech Conference
Anesthesiology for the Dental Profession
Institute for Vocational Rehabilitation of Mentally Ill

renewal of former skills, and acquisition of new knowledge is a need of all physicians, not of one group alone.

The prime responsibility of the Kansas program is the physician of Kansas but, feeling a regional responsibility and encouraged by a regional response, the department no longer regards the state boundaries as valid limitations to its activities.

No longer are all programs prepared exclusively for physicians. We now recognize the need for providing continuation education for ancillary medical personnel such as nurses, technicians, physical therapists, etc. More recently, we have assumed the responsibility for a fourth phase of medical education —namely, that of health education for the lay public.

TOTAL ENROLLMENT - - 3760	
Physician Enrollment	
Symposia	1417
Intermittent Courses	546
Correspondence Courses	299
Advanced, Clinical and Investigative Technics	53
Clinical Traineeship	4
Total Physician Enrollment	2319

Figure 1 — Physician Enrollment for 1955-56

The real aim of all medical education should be to improve the health of our people. Increasing the skills of all those engaged in medical care and increasing the understanding regarding health matters for those receiving the medical care are, therefore, prime objectives. This final statement indicates clearly our potential student body.

Scope and Structure of Present Program

An immediate view of this program can be gained from the course offerings and enrollment for the period of July 1, 1955, through June 30, 1956.

Local Attitudes Toward Postgraduate Education

During the past 10 years the Kansas program of postgraduate education has matured and has become effective and extensive as an enterprise in continuation education. This situation, however, came about after almost 40 years of effort. The most recent step in the program's development, and the one which gave it the greatest stability, was the creation of the Department of Postgraduate Medical Education within the medical school. This provided the needed

Allied and Ancillary Personnel Enrollment	
Doctors of Philosophy	6
Doctors of Dentistry	52
Medical Technicians	199
Registered Nurses	692
Lay Persons	492
Total Ancillary Enrollment	1441

Figure 2 — Non-Physician Enrollment for 1955-56

administrative structure. Of equal importance and coming earlier in the development of this program was the joining of efforts with the potential student body of the state medical society. These two features in origin would not have been sufficient without the whole-hearted acceptance by the dean of the medical school and the university administration of postgraduate education as a part of the responsibility of a medical school. This acceptance was outlined clearly by the administration in 1948 as a part of the Kansas plan for rural medical care.

Voicing publicly this responsibility of the medical school met with the spontaneous approval of the Kansas Medical Society, in such a manner as to impress every faculty member. It was an important step in renewing a desirable relationship with the practicing physicians within the state.

There has evolved in Kansas a working relationship between the state medical society and the medical school of the state university which has made possible an increasingly mature and extensive program of medical education. At no time in this relationship between the Society and the medical school has there been a conflict or friction which in any way impaired the prerogatives or fundamental policy of the school. The Kansas Medical Society through its Committee on Postgraduate Study has functioned as a helpful advisory committee and has at no time attempted to dictate policy. Such a pleasant relationship is in part the result of the medical school's approval of the over-all program, and of the real acceptance by the Society of this program as "their program," primarily designed for them with their help, and for which they have a paternalistic attitude.

The faculty of the School of Medicine has, by years of close association with the postgraduate program, become more sympathetic toward the additional burden of this phase of teaching. When the faculty was smaller resistance did exist, but it was lessened by the whole-hearted acceptance by the dean and the university administration of postgraduate education as a part of the school's responsibility.

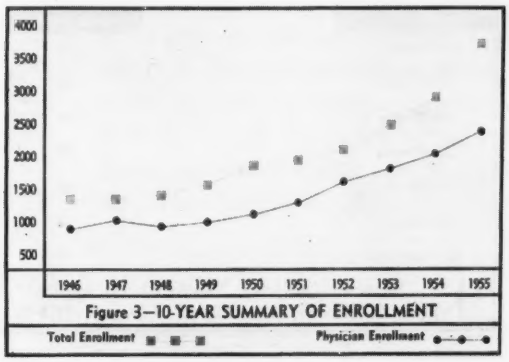


Figure 3—10-YEAR SUMMARY OF ENROLLMENT

PHYSICIAN ENROLLMENT FOR 1955-56	
Kansas	1096
Other States	1211
United States Territories	2
Foreign Countries	10
TOTAL	2319

Figure 4—ENROLLMENT GEOGRAPHY

Structuring a new Department of Postgraduate Medical Education with a departmental chairman, an executive director, and adequate personnel to do much of the routine work added a new dignity to the local program and administrative sanction to its permanence. All of this served to diminish the objections of the overworked undergraduate teacher who had not originally thought that such activities would be included in his duties. This was particularly true of the basic science instructors. Coloring the reluctance of this group was their inherent fear of disapproval when appearing before clinicians. Gradual fortification of the faculty with additional members, and inclusion in their initial interviews of a stipulation of responsibility to postgraduate education has overcome this problem. At present there is not a single member of any department of the medical school who does not willingly and frequently help with this form of teaching. One basic science teacher has, on several occasions, stated that he has never previously had such an excellent opportunity to assay the results of his undergraduate teaching.

The constant participation of basic science along with clinical teachers in teaching teams, both on the "circuit" and in "short courses," has done much to eliminate the schism between basic scientists and practicing physicians. It has vastly improved the morale of the basic science teachers by fostering a closer relationship with men who use their basic discoveries in daily practice. This team association has also done much to improve the level of teaching by the clinician, who all too often is quite off-hand in interpreting disturbed physiology and other basic phenomena, if there is no one about to check his enthusiasm.

The liberal use of "guest faculty" members for participation in all "short courses" lessens the burden on our own faculty, but the local faculty assumes full responsibility for the "circuit" programs as well as for the "clinical traineeships." For the "short courses" they assist with ward rounds, conferences, and panel

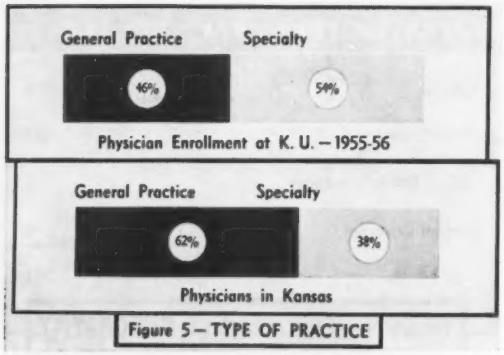


Figure 5 – TYPE OF PRACTICE

discussions, participating only occasionally in didactic presentations.

Distinguished guest faculty members have always been used in this program as a means of supplementing our own staff and of increasing program appeal and effectiveness. There is no question about the soundness and popularity of the practice, both among our faculty and the enrollees.

Self-Analysis and Evaluation

It will be said today that the ultimate aim of postgraduate education is the fostering of the best quality of medical care by each practicing physician. Therefore, it behooves an alert administrator in this field to appraise or inquire into the character and type of practice in the region served. He should learn of the needs and desires of his potential student body concerning program content, format, instructional staff, favorable dates for courses, and appropriate fees.

One can immediately appreciate the need for perpetual self-analysis and evaluation as elements in the continuation of successful operation of a program of postgraduate medical education. No medical administrator should be satisfied with organizing such a venture and then sitting back complacently to let it operate year after year without continuing study, appraisal, evaluation, and improvement.

This department has sought such information from its student body in several ways:

1. Questionnaires sent out by the medical society to individual practicing physicians inquiring about their own types of practice as well as about many of the common questions confronting a producer of postgraduate courses.

2. Registration data secured on each enrollee and tabulated annually, including: (a) city and state of practice, (b) field of practice, (c) medical school, (d) year of graduation, (e) distance traveled. This tabulation is subjected to continuous analysis.

3. An individual study of the patient material seen and treated by a group of representative general practitioners holding appointments as medical school preceptors is currently being carried out with the assistance of our medical student preceptees.

4. Each program produced is subjected to critical study by submitting to each enrollee a questionnaire concerning the specific program, its content, format, teaching techniques, fees, and suggested improvements.

Collection of registration data and "postmortem" information on programs is routine and continuous. The survey of medical practice in our state as well as the data regarding the individual practitioner, his training, his field of practice, etc. are special projects to be repeated at suitable intervals. Securing such information is essential to the success of a postgraduate program.

Physicians cannot be compelled to attend continuation study exercises, an impelling conscience being the only effective incentive. Only the American Academy of General Practice has had the courage to suggest more effective compulsion. The postgraduate student must be attracted to a program, and his interest must be captivated to hold him. His body cannot be captured as can the undergraduate's. The program must be sound, useful, and inspirational if he is to remain. It must promise the same for the future if he is to return. Programs must be planned carefully, promoted effectively, and produced well if they are to serve their purpose. This requires constant study and restudy of one's own problems. To date, there is no large and reliable clearinghouse of information or fostering influence to guide the school, department, or other producer of postgraduate medical education. Each must chart its own course.

Such useful data as shown in the following charts was gathered during the past year by the survey methods mentioned above.

Future

Looking to the future, we envision retention of the present administrative structure as a department in a

Distance Traveled	*Total Physician Enrollment*
Less than 25 miles	328
25-100 miles	186
100-200 miles	256
200-300 miles	360
300-500 miles	157
500-1000 miles	96
Over 1000 miles	60

Figure 6 – DISTANCE TRAVELED TO ATTEND POSTGRADUATE COURSES AT K. U. M. C.–1955-56

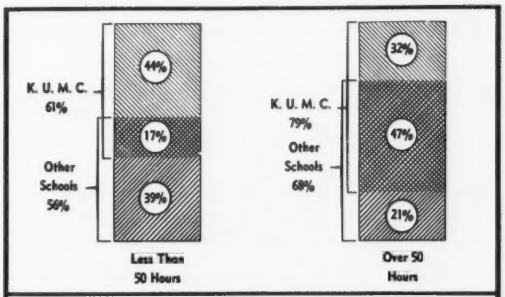


Figure 7—Place of Attendance for Postgraduate Study by Kansas Physicians—1953, '54, '55

medical school, using the same teaching staff, and retaining close identity with the parent medical school. Establishing a separate division or school would sacrifice something built deliberately—a teaching staff committed to all phases of medical education. The close liaison with the state medical society has been a major factor in the growth and security of our program, and retention of this relationship is essential.

Equally necessary is continued long-term planning of the programs of "intermittent" and "short" courses to fit the needs of the physicians of this region, with careful attention to curriculum material, effective methods of presentation, and selection of a competent faculty.

One of America's real contributions to medical education has been in the field of graduate medical education. Residency training is a proved method of giving, at least temporarily, a high degree of professional medical competence. The usual "short" and "intermittent" courses cannot be compared with it for effectiveness. This observation leads to a desire to increase our "clinical traineeship" teaching, simply because of the superiority of this method.

Acceptance of a fourth phase of medical education as a reality, and engaging in and assisting voluntary health organizations in health education we consider to be another important future objective.

We must continue the collection of data from registrants, the study of problems and practice of our student body. This sort of research and critical analysis is, at present, the only means available for evaluation and improvement of the program. Ultimate determination of whether a program is raising the level of medical care and inspiring the hoped-for response in the student body defies a direct approach. Further research in methods and modalities of teaching should represent another field of study for a progressive program. Increased use of television, the development of new "home study" courses, and exploratory courses in yet untried fields represent further possibilities in development.

Summary

The Kansas program of postgraduate medical education has, during the past 14 years, found new vitality and purpose. Most important in this change has been the association with the state medical society—the program's student body. Next in importance has been recognition by the university and the medical school of a prime responsibility for this phase of medical education. The school's acceptance took tangible form in the creation of a Department of Postgraduate Medical Education and giving it: (1) administration, (2) faculty, (3) facilities, and (4) budget. The department provided the remaining essentials: (5) curriculum, (6) teaching methods, and (7) self-analysis and evaluation.

The future will be secure if sound educational policies based upon continuing critical self-appraisal are maintained. Acceptance of the program is assured so long as the mutually profitable relationship with the student body is existent.

No man was ever endowed with a judgment so correct and judicious in regulating his life but that circumstances, time and experience would teach him something new, and apprise him that of those things with which he thought himself the best acquainted he knew nothing; and that those ideas which in theory appeared the most advantageous, were found, when brought into practice, to be altogether inapplicable.

—*Terence*

The Medical Center Library

Physical Properties and Service Potentials

G. S. T. CAVANAGH, ***Kansas City***

Few groups are more keenly aware of the importance of the printed word than workers in scientific medicine. A good library, properly staffed and housed, is essential to any institution engaged, as is the Medical Center, in medical education, research, and patient care. And access to books is necessary to any physician who wishes to continue his education on a personal as well as on a formal level. With the kind of support the Medical Center Library is now receiving, it becomes possible to offer library service outside the institution itself.

Libraries thrive on use and, also, on cooperation. Their ideal, obviously, is to make it possible for any medical worker to obtain any piece of medical literature, wherever and whenever published. To attempt to build complete collections all over the United States is neither feasible nor necessary. Instead, an unofficial system of service has grown up with the newly reorganized National Library of Medicine, Washington, D. C., at the head. Any physician may purchase microfilm or photostat copies directly from that institution, and any local library may borrow books and journals from it. But before this is done it is expected that local resources will be exhausted.

In practice this means that the Kansas medical man who has no direct access to a library should first apply to the Stormont Medical Library, State House, To-

Extension Service

Of the 28,000 books and periodicals loaned by the Medical Center Library last year, about three per cent went by mail to physicians, hospitals, and medical societies outside the university. In addition several thousand pages of photostats were supplied and a limited amount of bibliographical searching was carried on for the medical community of Kansas at large.

Requests for loans, photostats, or reference service should be addressed to the Reference Librarian, University of Kansas Medical Center, Kansas City 12, Kansas.

In requesting books and periodicals or photostatic copies, borrowers should send as complete bibliographical references as possible.

In requesting reference service, the problem should be stated fully and exactly, including the period to be searched; e.g. "no material more than ten years old."

An occasional publication, *Library Notes,* which includes a list of new books received, will be sent regularly to any physician or library on request.

The new Medical Center library building is expected to be in use by summer, 1957. Reading rooms, current books and journals, and the historical collection will occupy the two upper floors. Below ground will be space for an additional 90,000 volumes in open stacks.

peka, for the more common English-language medical literature. Failing this, he should apply to the Medical Center Library and, finally, to the National Library of Medicine. With a collection of 50,000 volumes and more than 900 periodicals currently received, the K.U. Medical Library is in a position to satisfy most requests.

Nevertheless, there is a great advantage to the local medical community in organizing and maintaining a current library of its own, however small. By pooling their resources a few men can gain access to 10 or 12 of the basic periodicals. For $25 a year the *Quarterly Cumulative Index Medicus,* or for $13.50 the *Current List of Medical Literature,* makes it possible for subscribers to select further material to borrow from the medical libraries. Hospitals, offices of county medical societies, or local public libraries can serve as clearing-houses for such loans. However, the Medical Center Library is willing to send material directly to any member of the Kansas Medical Society.

Obstetric Complications

Review of Brow, Chin, and Compound Presentations

LEROY A. CALKINS, M.D., *and*
EUGENE W. J. PEARCE, M.D., *Kansas City*

Brow, face (or chin), and compound presentation are all rather rare. Brow presentation has occurred about twice in each 1,000 patients in our series (including those patients referred to us because of the abnormal presentation). Chin presentation has been slightly less frequent, and the various forms of compound presentation, altogether, occurred in fewer than one in 2,000 patients.

Brow Presentation

Hellman, Epperson, and Connally[1] reported 44 instances of brow presentation in 65,930 deliveries, for an incidence of 1:1498. Posner and Buch[2] reported 13 "persistent brows" in 46,058 patients for an incidence of 1:3543. Our own material reveals 40 examples in 18,677 patients, or 1:468. This seemingly higher incidence can be accounted for only by a fairly early diagnosis in our series. We had no "persistent brows" such as were reported by Posner and Buck.

Both Hellman et al. and Posner felt that this presentation is more common in multigravida. Our own material shows equal frequency. Contracted pelvis (particularly the inlet) was frequently present in each of the above series. Minor flattening of the inlet was noted in only four of our patients. Gross developmental anomalies, as reported in the above articles and in some textbooks, have always been considered as one of the causes of this presentation. We had two instances of hydrocephalus. A large baby (over 4,000 grams) was present in one of 13 primigravida and in five of 27 multigravida in our series (relative disproportion?). Thus, while largeness of baby may be a factor in producing this presentation, it is not nearly so striking as in bregma presentation.

Hellman lists prematurity as a cause of extended presentation. Our material includes five infants (two barely so) under 2,500 grams, which is not more (perhaps less?) than the expected number. Dr. Frank P. Light, in discussing Hellman's paper said, "To us, brow is simply a transition phase." Obviously, the etiology, except for a few factors, is not yet clear.

In addition to statistical information reported from the literature, this study includes information on incidence of abnormal presentations, description of the course of labor, and a summary of results in patients seen in the Department of Obstetrics, University of Kansas Medical Center.

Course of Labor. In our series there were several instances of a long first stage of labor and a few instances of a prolonged first stage—all associated with weak and infrequent contractions. There was also a surprisingly large number of very short first stages—associated with frequent contractions of good intensity. That the abnormal presentation was provocative of weak and infrequent contractions in the former group would seem to be contraverted by the situation in the latter, larger group. As of now, it would seem that the first stage of labor is not markedly altered by brow presentation.

The second stage shows a picture unique to this presentation—

	Primigravid			*Multigravid*		
		Fetal			*Fetal*	
Type of Delivery	*No.*	*Deaths*	*%*	*No.*	*Deaths*	*%*
Spontaneous Conversion and Delivery	7	0	0	16	1*	6
Manual Conversion and Spontaneous Delivery	0	0	0	4	1††	25
Low Forceps	3	1**	33	1 HF	0	0
Combined podalic version	0	0	0	2	0	0
Cesarean Section (all done for other indications)	3	1†	33	3	0	0

* Hyaline Membrane.
** Eclampsia.
† Hydrocephalus—craniotomy after death.
†† Unknown.

It is quite striking, in this material, that there was not a single instance of failure of spontaneous conversion (to occiput in the majority) when given the opportunity. There was one instance of prolonged second stage (116 minutes) among the primigravid patients. (The remainder averaged 29 minutes.) In the multigravid patients there were four possibly prolonged second stages (not clearly documented), and the remaining 15 patients averaged 13 minutes.

The third stage was also normal. The duration in the first labors averaged six minutes, and the blood loss 170 cc. The multigravid patients averaged five minutes and 128 cc.

Results. One mother died of eclampsia. One other suffered a ruptured uterus, following a combined podalic version, and required hysterectomy and had a stormy recovery. There were seven instances of slight morbidity, one example of pyelitis, and one instance of puerperal endometritis (the craniotomy patient).

The fetal results (immediate) were uniformly good, except for the one infant (see unknown in above table) where manual conversion was followed by spontaneous delivery, and the baby died in a few minutes. Autopsy permission was obtained but, because of a misunderstanding, the examination was not performed.

Conclusions

1. Brow presentation is still not well understood.
2. It should be regarded as a "transitional" situation, in that the first stage will progress in the same fashion as an occiput presentation. In the second stage it will change to an occiput or face presentation and proceed accordingly.
3. Manual conversion cannot be said to be definitely indicated and can be said to be permissible only if readily accomplished.
4. Cesarean section should be performed only if otherwise indicated.
5. Combined podalic version should be discarded unless otherwise indicated.

Face Presentation

Face presentation, once it occurs either before or during labor, can be expected to persist; and, once diagnosed, it presents a definite entity. Its incidence, as usually recorded, is much more common than brow presentation but less common than transverse. Hellman reported an incidence of 1:468, Posner 1:529, Reddoch 1:550, and Rudolph 1:576. Light, in discussing Hellman's paper, mentioned incidence of 1:749 for colored and 1:606 for white patients. Our own material shows 1:602, which does not include those patients in whom the initial presentation was brow and spontaneous or manual conversion later resulted in a face presentation. The overall incidence would, therefore, seem to be slightly less than two per 1,000.

Etiology. A far forward axis of the uterus, disproportion due to contracted pelvis, or large baby, prematurity, and—most importantly—monsters of the anencephalic type are etiological factors stressed prominently in the literature. Nine of our 31 (not including two second twins) patients had fetuses weighing less than 2,500 grams. Two were anencephalic. Only two (multigravid) patients had babies in excess of 4,000 grams. At present we are not convinced of the role of the various named factors, except the obvious anencephaly. In our series 11 were primigravid and 20 were multigravid, (ten para three or more).

Course of Labor. We had two instances of prolonged labor, but the majority of the labors were remarkably short. The average of the first labors was 15 hours, and of the multiparas (excluding the two prolonged labors) was 7½ hours.

All patients were delivered spontaneously, except our cesarean sections done before complete dilation. The average duration of the second stage in first labors was 36 minutes, and in the multigravida it was 16 minutes. Of the ten primigravid patients proceeding to the second stage, five were anterior and five posterior positions. All rotated and delivered without assistance, except one delivered (by election) by combined podalic version after 27 minutes. Of the 16 multigravida, 13 were anterior. Ten of these delivered without assistance. Manual assistance (by election) to complete the rotation was used in two.

One patient was delivered by combined podalic version because of premature separation of the placenta. The three posterior positions rotated and delivered without assistance.

Most of the authors report that spontaneous delivery can be anticipated. Both Hellman and Reddoch pointed out a high percentage of failures of attempted conversions. Reddoch also stated that "versions and extraction should have no place in the delivery of face presentation except in the case of an occasional second twin." Rudolph states, and the data of the other reporters would so indicate, that cesarean section is the procedure of choice in the small percentage of patients requiring operative intervention.

Results. Maternal mortality and morbidity can be markedly increased by complicated vaginal manipulation. Several deaths are reported in the literature. Uterine ruptures associated with combined podalic version and lower genital tract trauma from extensive, and often forceful, vaginal manipulation are also reported. In our patients there was one instance of pyelitis and six minor temperature elevations in primigravid patients and one instance of cystitis and one minor temperature elevation in multigravida.

Fetal mortality has been generally reported between 15 and 25 per cent. In our series there was one ante partum death (in a primigravida) for which no cause was found clinically or at post mortem. One other baby died intra partum from compression of the umbilical cord. In our multigravida, there were two deaths from anencephaly, one death from premature separation of the placenta, and two deaths (at three days) from pneumonia. No death, save possibly that caused by cord compression, would seem to have been due to malpresentation.

Conclusions.

1. The etiology of face presentation, except for the obvious factor of anencephaly and anterior neck masses (thyroid tumor or interposed upper extremities) is not too clear.

2. The clinical course of labor, as demonstrated by the reports in the literature and our own material, will not be markedly different than for occiput presentations.

3. Chin posterior, as taught long ago, will almost never fail to rotate anteriorly and deliver spontaneously if given an opportunity to do so.

4. Combined podalic version should have no place (except in second twins) in the management of this presentation.

5. Attempts at conversion are unnecessary and are apt to fail.

6. In the event that operative delivery seems necessary (a small minority) cesarean section is the procedure of choice.

Compound Presentation

Compound presentation (usually occiput presentation with prolapsed hand) is the rarest of all presentations. We would list nine such cases with two others in second twins, and one instance in a patient admitted after 60 hours in labor and multiple attempts at delivery in another hospital. It seemed to us, from incomplete data, that the hand had been pulled down by the manipulations. This patient had a dead fetus, which we delivered by craniotomy. She had pre-eclamptic toxemia and developed puerperal endometritis, but she recovered. The two examples in second twins were delivered successfully by combined podalic version.

The other nine cases present an interesting picture. Five of the nine had fetuses varying from 1,010 grams to 1,775 grams: No. 1, 1,010 grams, normal labor, died in a few hours from intracranial hemorrhage; No. 2, 1,100 grams, normal labor, normal baby; No. 3, 1,280 grams, prolapsed cord, died in three hours; No. 4, 1,720 grams, ante partum death, placenta previa; No. 5, 1,775 grams, ante partum death due to premature rupture of membranes and prolapsed cord.

Four instances only have been observed at term. In one case, a cesarean section was done early in labor because of a prolapsed cord, with successful delivery of a 3,380 gram infant. The other three (2,985, 3,050, and 3,320 grams) were delivered spontaneously after short and perfectly normal labors. One of these three infants had a considerable necrosis and slough of the forearm tissues, which healed slowly and resulted in some contracture (no subsequent follow-up).

It would seem that compound presentation does constitute an infrequent problem, and we have little concept of its importance.

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Cerebrovascular Disease

Medical Management of Thrombotic and Embolic Lesions

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Cerebrovascular diseases rank among the major causes of death or disability in the western world today. Unfortunately, they affect not only the aged but also many individuals in the middle decades of life. Twenty-five to 50 per cent of all "strokes" occur in persons below the age of 65.[1, 2]

In the past, cerebrovascular accidents were treated in an expectant manner with a somewhat fatalistic attitude. It is true that little can be done to alter the high immediate mortality following cerebral hemorrhage, although an occasional selected case may be salvaged by surgical intervention. Recently encouraging results have been observed in the management of cerebrovascular diseases with anticoagulants. The subsequent discussion deals primarily with this latter group of cases.

Etiologic and Pathologic Considerations

About one-half of all cerebrovascular accidents are hemorrhagic. Another 40 per cent are due to thrombosis, and the remaining 10 per cent are due to cerebral embolism.[3]

Cerebral thrombosis seldom forms except where there is atherosclerosis. The large arteries at the base of the brain are involved earliest and most severely by atherosclerosis, especially at points where arteries bifurcate, branch, or curve sharply.[4]

Several factors predispose to cerebral thrombosis. Systemic hypotension may decrease cerebral blood flow and precipitate thrombosis during surgical anesthesia, in shock from hemorrhage or acute myocardial infarction, and occasionally in elderly persons following the drastic reduction of blood pressure with hypotensive drugs. Marked hemoconcentration resulting from dehydration, massive diuresis, or shock may so increase blood viscosity as to promote thrombosis.

Cerebral embolism usually originates from a mural thrombus in the left side of the heart. At least one-third or more of patients with acute myocardial infarcts who have not received prophylactic anticoagulants form mural thrombi in the left ventricle, especially in the presence of a large infarct, co-existing shock, or congestive cardiac failure.[5] Thromboembolic cerebrovascular lesions were found at autopsy in approximately 10 per cent of 210 cases of acute myocardial infarction studied by one of us.[6]

Left atrial mural thrombi are common in rheumatic mitral valvular disease, particularly when there is auricular fibrillation or congestive cardiac failure.[7] In a study of 194 patients with rheumatic heart disease and systemic arterial embolization, Daly and his associates found 64 deaths from cerebral embolism.[8]

Bacterial endocarditis involving the aortic or mitral valves is often the source of multiple arterial embolizations. Many such emboli are septic and may result in the formation of a brain abscess in the case of cerebral embolism.

The general clinical picture of thrombo-embolic cerebrovascular diseases has been discussed, emphasizing the differential diagnosis from cerebral hemorrhage and from intracranial neoplasms.

The syndromes of intermittent insufficiency of the basilar arterial system and of the internal carotid arterial system are briefly described.

The medical management of certain cerebrovascular lesions with anticoagulants and vasodilating drugs is discussed.

The extent of damage to the brain after cerebrovascular occlusion depends upon the adequacy of collateral circulation, upon intracerebral blood pressure and blood flow, and upon the speed with which occlusion has occurred. Gradual closure of a cerebral artery may allow more chance for collateral channels to be opened than if occlusion has been sudden and complete. Severe arteriospasm may follow sudden peripheral arterial occlusion. Insufficient evidence exists to assess the importance of arteriospasm in the brain following cerebrovascular occlusion, although certain pharmacologic agents are known to increase cerebral blood flow, presumably by vasodilatation.

Clinical Picture and Differential Diagnosis

When anticoagulant therapy of cerebrovascular accidents is considered, it is essential to distinguish

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TABLE I

DIFFERENTIAL DIAGNOSIS OF CEREBROVASCULAR ACCIDENTS

	Hemorrhage	*Thrombosis*	*Embolism*
Onset	Sudden, often after exertion, or during day	Often gradual, at night, or after episode of hypotension	Sudden
Associated Hypertension	95% Hypertensive	75% of CVA's in normotensives are thrombotic	Hypertension only coincidental
Associated Heart Disease	May have hypertensive heart disease	Common, but not usually causative	Usually mitral stenosis or myocardial infarct
Headache	65% of Cases	5-10% of Cases	25% of Cases
Vomiting	50% of Cases	5-10% of Cases	25% of Cases
Convulsions	20% of Cases	5% of Cases	5-10% of Cases
Coma	Frequent, often progressive	Less common, often transient	Less common, usually transient
Stiff Neck	Often severe	Rare	Rare
Neurologic Signs	Diffuse, severe, often progressive	Hemiparesis most common	Discrete, localized signs
Leukocytosis	Often marked	Rarely severe	Rarely severe
Glycosuria	Often with intracranial pressure increased	Seldom in non-diabetic	Seldom in non-diabetic
Cerebrospinal Fluid (CSF)	Pressure often high, bloody or xanthochromic 85%	Pressure normal Fluid clear usually	Pressure normal Fluid clear usually

hemorrhage from thrombo-embolism, since these agents may aggravate hemorrhage. Usually the diagnosis of hemorrhage is not difficult; occasionally, however, absolute clinical differentiation may be impossible. The principal differential features of the three major types of vascular lesions are summarized in Table I.

If there is any doubt concerning the exact nature of a cerebrovascular accident, a lumbar puncture should be performed and the cerebrospinal fluid examined. This examination should be performed in every case in which anticoagulant therapy is anticipated to exclude the probability of hemorrhage. Some authorities have warned against doing lumbar punctures in cases of cerebral hemorrhage showing signs of increased intracranial pressure because of the alleged danger of causing herniation of the uncus or brain stem. Usually the diagnosis of hemorrhage in such a patient is so obvious that lumbar puncture is unnecessary; however, minimal danger exists if the examiner avoids multiple penetrations of the dura, uses a small needle, and withdraws slowly only 5 ml. of fluid. If the cerebrospinal fluid specimen is bloody, it should be centrifuged and the supernatant fluid examined. The supernatant fluid becomes bloody within a few hours after a hemorrhage, while if the bleeding is due to a traumatic puncture, the supernatant fluid will be clear.

The focal neurologic signs produced by cerebrovascular accidents are dependent upon the areas of the brain affected and do not differ from the signs caused by non-vascular lesions in the same locations. In general, the neurologic signs of cerebrovascular lesions are fully developed within the space of a few hours or days at the most, whereas the signs of intracranial neoplasms tend to develop gradually and progressively over a much longer period.

When the cerebrospinal fluid protein level is 100 mg. per cent or more, the diagnosis of an intracranial neoplasm is heavily favored. Hemorrhage into the subarachnoid space will increase the cerebrospinal fluid protein content. The true concentration of cerebrospinal fluid protein may be roughly calculated by deducting 1 mg. per cent for each 750 erythrocytes per cu. mm.

Some of the cerebrovascular syndromes are manifested by transient signs occurring over periods of weeks to months closely simulating the symptoms of expanding intracranial masses, especially if there are convulsive episodes. Absence of phenomena in-

duced by increasing intracranial pressure such as tonic or clonic seizures, altered consciousness, radiographic or electroencephalographic changes, tends to exclude the probability of expanding intracranial masses. If other means have not clearly delineated the diagnosis, cerebral arteriography should be performed.

There are two cerebrovascular syndromes which experience has shown are particularly responsive to anticoagulant therapy, namely, the syndromes of intermittent insufficiency of the basilar arterial system[9, 10] and of the internal carotid arterial system.[11, 12]

The basilar arterial system distributes blood to the brain stem and to the occipital lobes via the posterior cerebral arteries. Characteristically the syndrome of basilar arterial insufficiency is manifested by a variety of neurologic symptoms occurring in sharply episodic attacks as listed below:

1. Transient visual symptoms—homonymous field defects, diplopia, ptosis
2. Temporary mental confusion, clouding, or loss of consciousness
3. Attacks of true vertigo
4. Transient disturbances of speech
5. Dysphagia
6. Episodes of vomiting and headache
7. Transient hemiparesis or hemiplegia
8. Transient sensory phenomena involving one side of the face, one extremity, or one-half of the body.

The diagnosis should be considered especially when any of the symptoms listed occur on different sides of the body during different attacks: e.g., hemiparesis on the left side of the body in one attack and on the right side of the body in a subsequent attack.

The internal carotid arterial system transports most of the blood supply to the ophthalmic arteries and to the cerebral hemispheres excepting the occipital lobes. The symptoms of internal carotid insufficiency are usually those of episodic, homolateral disturbances of vision associated with transient motor or sensory dysfunction on the contralateral side of the body. The principal manifestations of internal carotid insufficiency are listed below:

1. Transient visual disturbances—monocular loss of vision on same side as the lesion
2. Cerebral hemispheric disturbances—manifested on the side of the body opposite to the lesion
   a. Transient hemiparesis or hemiplegia
   b. Transient sensory phenomena in the face or extremities
   c. Focal or generalized epileptic seizures
   d. Periods of mental confusion or unconsciousness.

Occasionally it is possible to demonstrate the absence of an internal carotid pulse by inserting a finger into the postero-lateral pharynx, which of course aids the diagnosis. Usually this method is difficult and unreliable. If there is any reasonable doubt concerning the diagnosis, a cerebral arteriogram should be done.

Treatment

The anticoagulant drugs appear to be the most effective agents in the prophylaxis and treatment of thrombo-embolic cerebrovascular disease. Long-term studies by several authors[2, 10, 12, 13] have demonstrated that properly controlled anticoagulant therapy will usually prevent the formation or propagation of thrombo-embolic lesions in the cerebral vessels. There is some evidence to suggest that these agents will also promote recanalization of existing thrombi.[13]

At present, the indications for the use of anticoagulants in the treatment of cerebrovascular disease[14] are:

1. Recurrent cerebral emboli
2. Intermittent insufficiency or thrombosis of the basilar arterial system
3. Intermittent insufficiency or thrombosis of the internal carotid arterial system
4. Possibly for recurrent cerebral thrombosis elsewhere in the brain.

Effective, safe anticoagulant therapy requires the availability of a competent laboratory equipped to perform accurate prothrombin and clotting times; an alert physician who is well informed in the use of these agents; and a reasonably intelligent, cooperative patient. Anticoagulant administration is absolutely contraindicated in the presence of bleeding anywhere in the body and particularly if there is cerebral hemorrhage.

Heparin is generally given during the first two or three days because of the rapid onset of its anticoagulant effect. Daily measurement of the venous clotting time should be done when heparin is used, the optimum level being between 20 and 30 minutes. Therapeutic effects are usually obtained by the intravenous administration of 50 mg. crystalline heparin every three to four hours.

We seldom use the so-called depot-heparins because we have found difficulty in maintaining the clotting time within the limits defined with these preparations. Recently a concentrated crystalline preparation of heparin containing 200 mg. per ml. has become available. Limited experience with this product has been gratifying in that we have usually been able to maintain the clotting time in the therapeutic range with an intramuscular dose of 75 to 150 mg. every 12 hours. Each individual patient's dose must be assayed. Heparin administration is discontinued whenever the prothrombin level has

been adequately reduced by the use of other delayed action agents.

Administration of the longer-acting prothrombin depressing drugs is begun concurrently with the first dose of heparin. For at least the first two weeks of therapy, the prothrombin time should be measured daily. Safe therapeutic levels of the prothrombin time are between 10 and 30 per cent (or, if reported in seconds, the patient's time should be 2½ times the control time). Ethyl biscoumacetate (Tromexan®) effectively reduces prothrombin activity within 24 to 36 hours, and the patient is often given one dose of 900 to 1,200 mg. to depress the prothrombin level while waiting for the activity of bishydroxycoumarin (Dicumarol®) to become evident.

Dicumarol is the drug we prefer for long-term use, although there are numerous others which appear to be equally as effective. The average initial oral dose of Dicumarol® is 300 mg. to be followed by 200 mg. on the second day and often by 100 mg. on the third day. Subsequent daily maintenance doses usually vary from 25 to 75 mg.

After the patient has been stabilized on Dicumarol® therapy in the hospital for about two weeks, it is generally possible to determine an average daily dose, following which the patient may be sent home. His prothrombin time can be measured at weekly intervals on an out-patient basis. Such a patient must be carefully instructed to report immediately any hemorrhagic tendencies such as epistaxis, purpura, or ecchymosis, hematuria, melena, etc. This treatment should be continued indefinitely in the patient with thrombo-embolic cerebrovascular disease. We have observed several such patients who stopped their anticoagulants for various reasons and shortly thereafter experienced recurrence of symptoms.

Once the existence of cerebrovascular insufficiency or occlusion has been established, it is desirable to stimulate increased cerebral blood flow as well as to prevent further intravascular coagulation. Only two pharmacologic agents are known to increase cerebral blood flow. Inhalations of carbon dioxide 5 per cent with oxygen 95 per cent may increase blood flow through the brain by as much as 75 per cent. Frequently it is administered to the patient by face mask five or ten minutes every hour during the day.

Increases of cerebral blood flow up to 20 per cent have been observed with use of papaverine. This drug is usually given subcutaneously 30 to 60 mg. every six hours, or its synthetic counterpart, dioxyline phosphate (Paveril®) is given orally 100 to 200 mg. every six hours. Despite its popularity, nicotinic acid has no effect on human cerebral blood flow, and two other frequently used drugs, aminophyllin and caffeine, may actually reduce cerebral blood flow.

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Laws have their proper place, but the responsibility of worthy citizenship is a personal one. We each have a separate and individual share in eradicating social evils and in refusing to perpetuate practices odious to a free nation.

—Herbert Brownell, Jr.

Respiratory Insufficiency

A Grave Problem in Newborn Infants

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Severe respiratory insufficiency in newborn infants is not an infrequent occurrence, especially among premature infants. Almost all of the deaths during the first week after birth are the result of respiratory insufficiency, caused either by cerebral disturbances or abnormal conditions in the respiratory tract.

Clinical methods for grading the degree of respiratory insufficiency in newborn infants have not been accurate. Attempts to evaluate the amount of cyanosis, dyspnea, hypotonia, or edema by clinical methods have been fraught with error, because of the large subjective element necessarily involved.

An explanation is given for high morbidity and mortality rates, along with an explanation of aberrations in respiratory rates, in infants afflicted with respiratory insufficiency. The plan of therapy at the University of Kansas Medical Center is outlined.

Recent studies in this clinic indicate that newborn infants can be classified as normal or as having mild or severe respiratory insufficiency by determining the course of the respiratory rate beginning at birth and continuing for the next two or three days.[1, 2] Classification by this method helps not only in predicting survival but also in planning oxygen therapy. The need for careful use of oxygen in the treatment of neonatal respiratory insufficiency in small premature infants has again been recently emphasized, in order that the severe consequences of retrolental fibroplasia may be kept at a minimum.[3]

Respiratory rates in newborn infants can be classified into three groups according to their trends. Group I includes infants who breathe at a rate of approximately 40 per minute at birth and continue to breathe at about this rate throughout the neonatal course. Infants in Group II breathe at a high rate initially, and then the rate falls to normal levels during the next day or two and remains there. No infants in this clinic belonging to Groups I and II have needed oxygen therapy or died, irrespective of how little or how much they weighed at birth.

Infants in Group III often demonstrate severe degrees of respiratory insufficiency. Their respiratory rates may be low, normal, or high right after birth, but in every instance there is a significant increase in respiratory rate sometime during the first 48 hours. In this clinic about 50 per cent of the infants in Group III have required oxygen therapy, and about 25 per cent have died during the early neonatal period.

The explanation for the three trends of the respiratory rate described above and for the high morbidity and mortality observed among infants in Group III is to be found in part in studies done on the physiology of neonatal respiration. Resting tidal volumes apparently are greater among infants in respiratory Groups I and II than in Group III.[4] The larger tidal volumes among infants in Groups I and II suggest a more rapid expansion of their lungs and probably account for the fact these infants are able to attain satisfactory saturation of their blood with oxygen a few minutes after birth and to overcome any tendency to respiratory acidosis within two or three hours of their birth.[5] Conversely the low resting tidal volumes observed among infants in Group III suggest a poor expansion of their lungs, a fact borne out by postmortem examination, and also help explain why some of these infants are unable to saturate their blood satisfactorily with oxygen the first day or two and tend to have a marked respiratory acidosis. Some of these infants occasionally have increases in the tension of carbon dioxide and decreases in the pH of their blood that are alarming.[6, 7]

The combination of respiratory acidosis and hypoxemia in the newborn infant is interesting because hypoxia apparently does not act to stimulate respiration in this age group as it does later in life. In fact moderate hypoxia appears to depress the newborn infant.[8, 9] The depressing effects of moderate hypoxemia would explain why some newborn infants, especially premature infants, have apnea and bradypnea immediately following birth.[10] As the hypoxemia becomes less, the stimulating effect of an increase in tension of carbon dioxide would very likely make itself felt, thus perhaps accounting for the increase in respiratory rates in infants belonging to Group III.

The above explanation satisfactorily accounts for

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the aberrations in the respiratory rates seen during the first day or two among infants in Group III. However, the problem confronting these infants is more complex than described above. In order to facilitate the explanation of their respiratory difficulty, the course of events has been schematically represented (Figure 1). This schematic presentation is based on studies done in this clinic. The presumed course of events for a hypothetical infant in Group III has been compared with that of a hypothetical normal infant (Group I).

The point to be emphasized is that infants in Group III can recover from the initial respiratory difficulties of the first day or two. Their respiratory rates decline to normal levels; their blood is well saturated with oxygen; acid-base balance becomes normally adjusted. The infants often appear clinically well. Actually many of them are not, and a considerable proportion eventually die before the end of the first week, especially those who weigh less than 1,750 grams at birth.

The explanation seems to lie in the fact that although they appear to have recovered fully, their lungs remain only partly expanded. Measurements of resting tidal volumes continue to be low throughout the first week and often extending into the second week. As shown in the graph, their recovery comes about in spite of the fact their tidal volumes do not appreciably increase. Their improvement presumably takes place because of a relative increase in effective alveolar ventilatory space and decrease in dead space.[11] It is also possible that some improvement occurs in the diffusion of gases across the alveolar wall as the result of changes in the wall itself. In any case the tidal volume apparently increases but little.

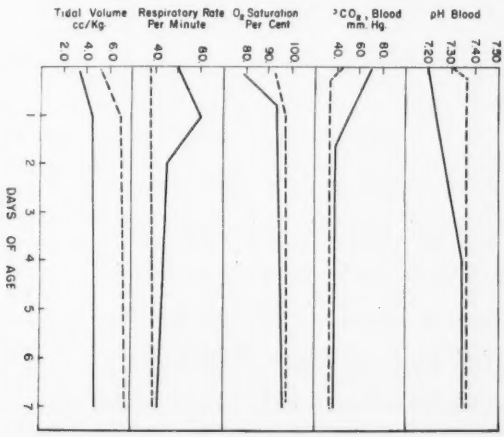

Figure 1. Changes in respiration, blood-gas determinations and pH of blood in a hypothetical infant with respiratory insufficiency (Group III)———— compared with those in a hypothetical normal infant (Group I) ------.

These infants remain in jeopardy so long as their tidal volumes remain small, since very little encroachment on the tidal air space would be required to tip the scales against them. Usually it is the small premature infants who are most apt to get into serious difficulties during this period of apparent recovery. The difficulties often come suddenly and without warning in the form of severe bradypnea and apnea. If the infant dies during this period, autopsy may show a cerebral hemorrhage several days old, evidences of pneumonia and rather marked atelectasis, kernicterus, or sepsis. It is easy to believe that any one of these findings could tip the balance against the infant. What is difficult to explain is how some of these infants can appear to be so well during the so-called recovery period.

One additional fact is pertinent. Gross irregularities of respiratory rhythm characterize the breathing of premature infants during this recovery period. The cause of the irregularity is not known. The infants who die seem to be those with the greatest irregularities in rhythm as determined by measurements of the periods of apnea.[12] Some warning of impending disaster can be obtained by noting the length of the periods of apnea from which the infants recover spontaneously. If these periods exceed 30 seconds, the infant is in grave danger of having a more prolonged period of apnea from which recovery may not occur.

Any newborn infant may develop respiratory insufficiency. In this clinic the incidence of severe respiratory difficulty is comparatively low among infants with birth weights over 1,750 grams.[10] About 80 per cent of infants in this clinic who weigh between 1,001 and 1,750 grams can be expected to have severe respiratory insufficiency.

Individual respiratory records are kept on all premature infants in this hospital and on any full term infant thought likely to have trouble until all danger is past. The record starts at birth, and the respiratory rate is counted for a full minute every 15 minutes during the first hour, every two hours for the next 47 hours, and every four hours for the next two days. More frequent observations are made on critically ill infants and are continued for as many days as thought desirable. Respiratory rates obtained on restless and crying infants are discarded except during the first hour, when some restlessness is almost universal.

Particular attention is paid to the records of infants weighing less than 1,750 grams at birth. This is the group that has a high incidence of respiratory insufficiency and also is the group most likely to suffer from too much or too little oxygen therapy. Experience in this clinic has shown that if infants under

1,750 grams do not initiate sustained, spontaneous respirations within two minutes of birth, or do not attain a respiratory rate of 40 or more per minute during the first hour, they invariably develop significant increases in their respiratory rates and have a mortality of at least 50 per cent.

Observations on the trend of the respiratory rate have been helpful in planning oxygen therapy in this clinic. We believe oxygen therapy can be safely withheld from infants who weigh less than 1,750 grams at birth provided that they (1) are free of cyanosis within a few minutes of birth, (2) initiate sustained, spontaneous respirations within two minutes of birth, (3) attain a respiratory rate of 40 or more per minute in the first hour, and (4) do not have a significant increase in respiratory rates after the first hour. Concentrations of oxygen are kept at 40 per cent or less for infants needing oxygen therapy.

Concern over the production of retrolental fibroplasia by prolonged oxygen therapy or too high concentrations of oxygen is much less among infants who weigh more than 1,750 grams at birth. These infants receive oxygen therapy if they are cyanotic. Cyanosis is seen only in those who have significant increases in respiratory rates.

Indications for starting oxygen therapy are far more definite than those for discontinuing it. Small premature infants belonging to Group III are prone to develop severe apnea and bradypnea suddenly and unexpectedly even though they appear to have recovered from their initial respiratory difficulties of the first day or two. Criteria for ending oxygen therapy will continue to be indefinite for small premature infants until more reliable means have been found for predicting these sudden bouts of prolonged apnea and severe bradypnea.

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America can continue to be the source of emotional and moral strength for the world on one condition. That condition is that this nation stays prosperous, progressive, civilized; that our program of justice moves progressively forward; that we continue to reduce the areas of injustice within our borders. The great challenge of the century is to find ways and means of extending a practical program of justice to the farthest reaches of the world.

—*William O. Douglas*

Anorexia Nervosa

A Study of Residential Treatment

HARRY G. GIANAKON, M.D., ***Kansas City***

Residential treatment affords singular opportunity for the study and validation of basic psychopathology in emotionally disturbed children, and it also serves to clarify the dynamics of psychologically determined illnesses. The utilization of this approach resulted in the successful therapy of two children with anorexia nervosa (compulsion feeding neurosis) and in the uncovering of core fantasies undergirding their illnesses.

The psychologic concomitants of this disease have long been recognized. Morton,[1] in 1694, referred to this "consumption of mental origin." Much later Sir William W. Gull described emaciation "to the last degree through hysteric apepsia."[2] He then presented the classic description of what he termed "anorexia nervosa," characterized by repugnance to food, extreme emaciation, amenorrhea, and personality changes.[3]

It remained for modern workers to describe the specific personality changes most frequently encountered. Their reports hold this illness to be a graphic illustration of the influence of emotion on bodily functions and indicate that it is primarily a psychologic disturbance with physiologic concomitants, rather than the reverse.[4] Additional investigations underscored the basic anxiety and depression to be found and especially emphasized the compulsive obsessive features.[5] Actual loss of appetite was demonstrated as a rare occurrence; rather, the individuals do not eat because they are afraid to eat.[6] The term anorexia is, therefore, inappropriate, and the newer term, compulsion feeding neurosis, rapidly evolved.[7]

More currently there has been an interest in observation and treatment of individuals with this illness in medical hospital settings which are reinforced with psychiatric orientation. In severe cases, life is so threatened that management outside of a hospital is ill advised, and extreme care and attention to every facet of the illness is imperative if life is to be saved. All of these observations emphasize the difficulties that are encountered in daily management because of the psychologic limitations of the ill individual to respond to the regime, and, in addition, because of the limited psychiatric facilities of medical wards.[8] Large series of patients have been studied, and only in rare instances have basic fantasies been uncovered.[9]

This study was carried out in the Children's Residential Treatment Center of the Neuropsychiatric Institute of the University of Michigan, a children's psychiatric ward in a general medical hospital setting. It is a unit of 20 beds, and the children who are patients range in age from 6 to 14. The program is administered by a staff of nurses trained in residential treatment methods. School, occupational therapy, recreational therapy, and special reading opportunities are incorporated in the ward experience of each child.

A brief history of the evolution of current thinking in regard to compulsion feeding neurosis is attempted. Early awareness of psychologic concomitants of the illness and the modern work of specific study of personality changes are traced. Hospital management of this illness is presented, particularly children's residential treatment in a general hospital setting. Two cases are discussed to illustrate treatment of underlying impregnation fantasies.

The keystone of treatment is individual psychotherapy. Every effort is made to coordinate and integrate every ward function so that the individual psychotherapeutic experience is nurtured and strengthened. Frequent group and single staff conferences are employed to achieve this goal.

Two children with compulsion feeding neurosis were treated in this setting. One was hospitalized for a period of nine months, the other for a period of eight days. Through their response to treatment, they illustrate the value of both long- and short-term stays in a children's psychiatric ward of a general hospital.

Case Reports

Case 1: Robin P. D., age 12, began having difficulty following a tonsillectomy performed in October, 1950. There had been a gradual diminution of his appetite and eating shortly before this time, but the problem assumed major proportions following the surgical procedure. At school the boy displayed in-

Presented in a "Workshop on Anorexia Nervosa" at the 1956 annual meeting of the American Orthopsychiatric Association. Dr. Gianakon is assistant professor of psychiatry and pediatrics and director of the Child Study Unit at the University of Kansas Medical Center.

creasing weakness and inability to keep up with his studies. School authorities became extremely concerned when the boy would collapse in a limp fashion on the floor of the classroom.

A physician was consulted and informed the parents that Robin was suffering from a "small stomach ulcer." Following several weeks of Sippy diet treatment the boy was pronounced well, but the family noted no improvement in his condition. He was so weak that he was unable to go to school. He remained in bed and even was using a bed-pan for fear that he would collapse on his way to the bathroom. He was drinking a glass of milk daily, and this was the extent of his food intake. Concomitantly, the boy's behavior became extremely negativistic. He refused to speak to the other members of his family and would persist in "passive aggravation" in his relationship with his father. Finally the father insisted that the boy be removed from the home, and it was at this time that Robin was taken to the Children's Residential Center at the University of Michigan, in November, 1951.

The family history indicated that Robin's mother was suffering from a paranoid psychosis at the time of her marriage. Her illness had persisted throughout Robin's lifetime. The family had observed the mother during periods of hallucination when she would become quarrelsome toward imagined "union leaders" who, she felt, were plotting harm to her. Apparently Robin accepted this state of affairs without great question. When he was six years of age, the mother was confined to bed when she was discovered to have tuberculosis. She received pneumothorax treatment regularly, and this had been discontinued only during the year before Robin's hospital admission.

Until his illness, the boy slept with his mother. She insisted upon bathing him. Later he had objected to this and would allow her to wash only portions of his body. The boy had minimal contact with his father who would not come home from work until late at night, who slept in a separate bedroom, and who was gone early in the morning. The family gave the impression that the relationship with the father had been most noticeable since the boy's illness when his extreme negative teasing of the father became pronounced.

Laboratory data: Complete gastrointestinal x-rays failed to reveal the presence of an ulcer or any evidence that it had ever existed. Blood studies indicated hemoglobin of 85 per cent, nonprotein nitrogen of 40 mg. per cent, total serum cholesterol of 117 per cent. The basal metabolic rate was plus 6 per cent. Chest x-ray was negative. Skull plates and opthalmologic examination were negative. Psychologic testing revealed a "neurotic boy of potentially superior intelligence whose conflict is based on ambivalence concerning the expression of aggression and identification with males."

The course in the hospital was characterized, at first, by a continuation of his eating difficulties. He weighed 93 pounds on admission. He was almost totally non-verbal in his psychotherapeutic interviews and seemed to have great difficulty in forming positive relationships on the ward. There were reports of sex play with another boy on the ward. Following this, Robin had two "panic attacks" in which he became prostrate and manifested profound autonomic changes. He then confided that these were brought on following intense excitement due to sexual preoccupations with other children. On one of these occasions he had become stimulated in the occupational therapy shop as he watched one of the children working with a woodburning set. Accidentally Robin was burned slightly, and he became panic stricken when he felt that this had befallen him as a punishment for his thoughts.

When this episode was reviewed with him, he was able to verbalize his conception of sex and reproduction (Figure 1). He stated that everyone "had a baby inside." This baby remained quiet until one was in the presence of a "liked" person. In his thinking, this was substantiated by the fact that women who

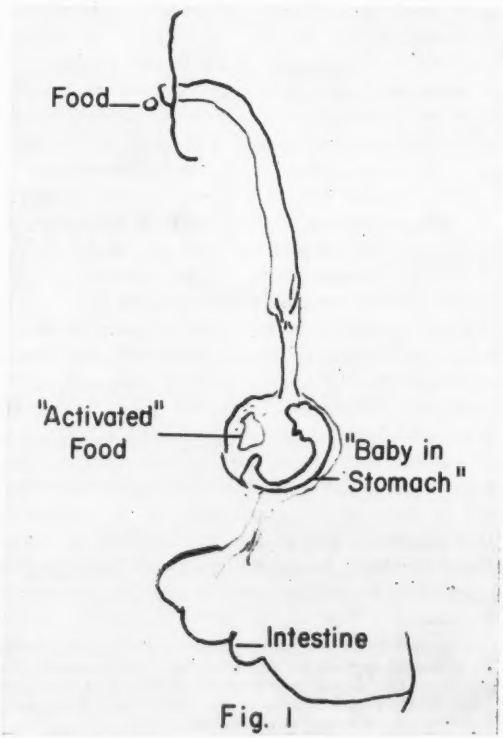

Fig. 1

had babies were usually married to someone they liked, although he realized this was not an imperative requirement. It was his feeling that the baby was activated by the ingestion of food. Food particles would be contaminated with "germs or something" of the "liked" person, and the baby would be activated. He was aware of the fact that men do not have babies. Yet, he felt, the process was very much the same. When the contaminated food was eaten by a man in the presence of someone who liked him, the "germs" would act on the stomach and form a "sore."

His fears were underscored when the consulting physician told his parents that Robin had a "small stomach ulcer." He recalled the tremendous anxiety he experienced then and his inability to discuss it with his parents. Subsequently he spontaneously asserted that there were two factors which had kept him from eating. First was the fantasy he had outlined. Second, he stated that he had not eaten solid food for two years and because he had gone without it for so long he was frightened that he would never be able to eat again.

In later interviews the boy disclosed a disturbed sexual relationship with his mother and confided that there had been considerable genital manipulation during the years in which he had slept with her.

All this while, the boy had been making a primary relationship with one of the attendants on the ward. The boy would immediately test the interpretations and insights gained in his interviews by applying them in this new found relationship. He would often request reassurance in the gradual formation of new attitudes. A consistency of approach was achieved by close association of the therapist and attendant. The boy became enthusiastically motivated in his social pursuits, and his eating gradually improved so that he was able to eat even in public restaurants without anxiety.

The parents were gratified by the boy's response and were cooperative in the formation of plans for Robin upon his discharge. Although of moderate circumstances, they agreed to Robin's placement in a midwestern private school. He has made a satisfactory adjustment there and his academic work has been of such quality as to make him an honor student. Although there are obviously continuing emotional difficulties, he is now able to maintain improvement with only an occasional out-patient visit.

Discussion: The neurotic symbolization of pregnancy fantasy through the gastrointestinal tract is obvious and needs no further elucidation. There appears to be confirmation, in Robin's history and treatment course, of the generally accepted theories that the primary gains received by the rejection of food are: (1) reluctance to mature and face adult responsibilities, (2) diminution and elimination of sexual desire through malnutrition which slows all biological processes, and (3) solution to a conflict with parents, with a masochistic device of atonement for the guilt that is aroused by this conflict.[10] In addition, the multi-phasic nature of symptoms is revealed. Symptoms may continue after the initial precipitating conflict has become secondary. The compulsion of habit may reinforce the symptoms and wreak further handicap on a weakened personality structure.

In treatment, the advantage of being associated with a general medical hospital seems clear. Parents, even if psychotic, first consult the medical physician when their child is ill. In Robin's case the initial contact with a physician was unfortunate and served to crystallize the boy's fantasy. Thus, an "iatrogenic" factor was added to the illness. This could best be resolved in a medical setting where the boy's cachexia could be overcome and where faulty diagnostic evaluations could be corrected.

The necessity for close staff integration is emphasized.[11] The importance accorded to every staff member's role increases the sense of participation and consequent enthusiasm for a common effort. A primary relationship was established by Robin for the ward attendant. The boy was immediately able to utilize and validate the insights gained in therapy and was confronted by a consistent and reassuring response at every test. The incorporation of ward reports and behavior in therapy made possible "on-the-spot" techniques[12] which facilitated his progress.

Chronologic maturation during residential treatment probably contributes to an improvement in relationship to the parents. The period of separation frees both child and parent from the over-burden of home adjustment, and the parents gain pride, prestige, and positive attitudes when the child can present his newly acquired achievements, behavior, and attitudes.[13]

Case 2: Dianne H., age 12, was a plump child, weighing 138 pounds. She began to have eating difficulties during the spring of 1951, when her mother became ill. Dianne had to assume some of the responsibilities of housework and waited on and cared for her mother while she was in bed. Because of the irregularity of the meals during this time and the fact that the mother was not able to prepare them as she formerly had, the family felt no undue concern over Dianne's eating problem. However, Dianne's refusal to eat continued after her mother's recovery.

At first Dianne would attempt no explanation for her eating habits, except to state that she was not hungry. Later she informed her mother that some of the boys in her school had been teasing her about her weight and she wished to go on a diet to become more

physically appealing. She lost weight steadily and progressively and had to be hospitalized on several occasions. On admission to the University of Michigan Hospital she weighed 86 pounds.

Her history indicated that Dianne had been indulged by her family. She had always been a submissive child and had never posed a disciplinary problem of any proportion. She had been a good student in school and had always exerted herself maximally. The parents' only concern was Dianne's difficulty in social relationships. It was obvious that the mother was the dominant person in the family. This was indicated by such facts as the mother's insistence that she do all the driving of the family automobile. Dianne seemed much attached to her father, although the contact with him was minimal.

Laboratory data: Examination of the blood revealed the following: 12.7 gms. hemoglobin, sedimentation rate 17 mm. per hour, and hematocrit 38 per cent. Serum cholesterol was 360 mgs. per cent. Chest x-ray was negative. Psychologic testing revealed "a distorted relationship and identification with the parents, with constriction and depression."

The hospital course was characterized by a dramatic improvement in her eating habits. She was hesitant to join in group activities at first but quickly became a leader in the various ward functions. She formed a rapid relationship to her therapist and was discharged to her home with arrangements for out-patient care. The physician in her city was advised of her condition and directed the medical regime on her return home.

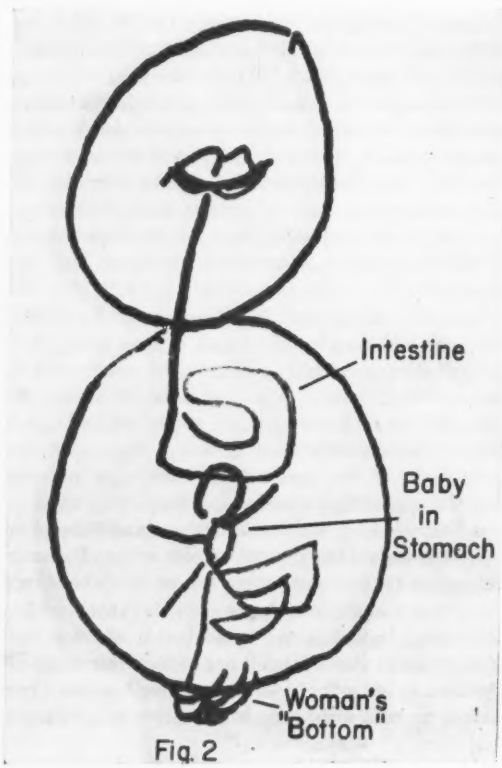

Fig. 2

During out-patient interviews Dianne told of a frightening experience which she had had shortly before the feeding difficulties began. She had felt kindliness and pity for an elderly man who lived in a "shack near the tracks" and who was shunned by the majority of the people in the neighborhood. On several occasions she took this man cookies she had baked in school. On one of these times he invited her into his "shack," embraced her, and made improper advances toward her. She ran away, panic stricken, and was too frightened to report this incident to anyone. Thereafter, she became preoccupied with sexual thoughts. These were heightened by the fact that she had observed her brother several times in the nude. In discussing her concept of reproduction, she drew a diagram illustrating her belief that a baby existed inside every woman (Figure 2). Her idea was that this baby would become activated either through the passage of "something" from the mouth through the "intestine" or from the passage of "something" through the "intestine" leading from a woman's "bottom."

As therapy continued, the parents were gratified by her increased social success at school. She gained in weight to 101 pounds, and this improved her physical appearance considerably. She was elected the class homecoming queen consort. She was also elected to the post of class treasurer. She is continuing in both academic and social achievements.

Discussion: It has been pointed out that children who are eating problems at home often become good eaters in a new environment. The removal of tension which pervades the home as well as the observation of other children who eat disliked food with relish possibly contribute to this.[14] Spoon feeding and intimate, personal attention at meals may be helpful.[15]

Although the child was admitted to the general hospital, the transfer to the Children's Psychiatric Ward quickly underscored the emotional factors of her illness for her. Each activity throughout the day was planned and purposeful and avoided her former hospital experiences of merely "sitting around from one meal to the next."[16] Upon her discharge home, her local physician was able to sustain her physical improvement and was able to countenance treatment suggestions without resentment because they emanated from a medical center.

Conclusion

The study and treatment of compulsion feeding neurosis are greatly facilitated and enhanced in the

setting of a Children's Psychiatric Unit of a general hospital.

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Ammonia Intoxication

The Theoretical Basis for Therapy with Arginine

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The importance of enzymatic reactions in the maintenance of life and health has become increasingly apparent in recent years. Many attempts to further elucidate the function, capacity, specificity, and other properties of enzymes are now in progress throughout the country. Transfer of the information thus gained, from the laboratory to the practicing physician, is frequently hindered by an unawareness of the properties of enzymes and their importance in human bodily economy. Illustration of how their properties have been recently applied to the therapy of ammonia intoxication is but an example of the promise such research holds for the future.

One of the most important properties of enzymes is the capacity of these biologic catalysts to operate through a wide range of activity. The magnitude or velocity of the reaction depends upon the concentration of the substance upon which the enzyme reacts—termed the substrate of the enzyme; thus, substrate concentration automatically regulates the degree of activity. The full implication of this truism has not yet been fully appreciated.

Two basic postulates apply to enzyme reactions in general and are germane to this discussion. As already indicated: (1) Enzymes can operate faster or slower, depending upon the availability of substrate, and (2) Generally the concentration of substrate is much smaller than the enzyme concentration.

A specific example may help to clarify these basic concepts. The enzyme, alcohol dehydrogenase, is present in normal liver regardless of the presence or absence of alcohol (illustrating Postulate 2). This concept is extremely important because it illustrates how bodily physiology readily adapts to changes in its environment.

This example of the clinical application of biochemical principles to the treatment of the syndrome of portal-systemic encephalopathy is illustrative of the promise that these basic concepts hold for clinical medicine. Elucidation of more of these fundamental enzymatic processes will undoubtedly provide newer and more efficient methods of therapy for many disorders.

However, ingestion of alcohol is followed by dehydrogenation of the alcohol by the enzyme. The velocity of this dehydrogenation reaction depends upon the amount of alcohol reaching the enzyme (illustrating Postulate 1).

Because enzymes are protein they are extremely

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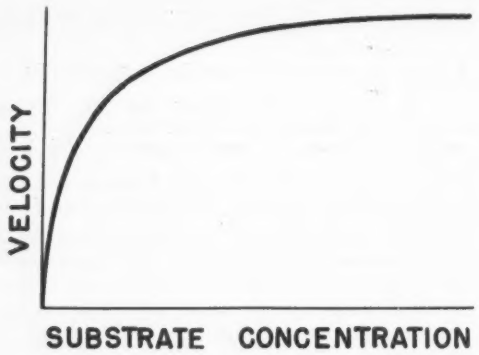

Figure 1.

complicated molecules and are but slowly synthesized by the cell. If the enzymes were operating normally near saturation, the response to increased substrate concentration would thus be limited. It would, therefore, severely restrict physiologic adaptability if the body were required to synthesize more or less enzyme according to the demands of substrate concentration.

With these fundamental concepts in mind, let us examine the clinical problem of ammonia intoxication. As is well known, ammonia is a very toxic substance, and accumulation of it in the body in excess of the ability to remove it via urea synthesis gives rise to a symptom complex which has been termed portal-systemic encephalopathy by Sheila Sherlock.

Portal-systemic encephalopathy thus arises from defective response of the body to a toxic insult. This defective adaptation may take origin from three general conditions: (1) The liver may be so injured that it is unable to remove even normal amounts of ammonia; (2) An overwhelming amount of ammonia may be presented to a moderately impaired liver, as for example with gastrointestinal bleeding, excess protein ingestion, or administration of ammonium salts; or (3) By administration of certain drugs, such as acetazoleamide, which block enzymatic pathways.

The defense of the organism to this metabolic insult may also follow one of three patterns. It may store ammonia as a non-toxic substance, such as glutamine. This possibility led to the use of mono-sodium glutamate in the treatment of ammonia intoxication. However, this mode of therapy has been disappointing, probably because of the poor permeability of the liver cell for glutamic acid[1] and the limited capacity of the body for the storage of glutamine.

A second mode of defense would be to increase the amount of healthy liver tissue and, in essence, the amount of enzymes involved in the removal of ammonia. For reasons already pointed out, this is a slow and relatively inefficient process that is inadequate in the acute situation. Moreover, protein synthesis is intimately dependent upon protein intake, and a cardinal rule in the treatment of ammonia intoxication is the elimination of protein from the diet.

The third, and most clinically adaptable, mode of defense is to increase the capacity of the enzymes involved in the removal of ammonia as urea. Four basic reactions are directly involved in the removal of ammonia as urea and are illustrated in Figure 2. A fifth pathway is also of indirect importance in this regard and is appended in Figure 2. The entire urea cycle and its interrelationship to the Kreb's citric acid cycle are graphically illustrated in Figure 3.

REACTIONS OF THE UREA CYCLE

1. Carbamylglutamic acid + NH_3 + CO_2 + ATP ___ Compound X
2. Compound X + Ornithine ____ Citrulline
3. Citrulline + Aspartic acid ____ Arginine + Fumaric acid
4. Arginine ____ Urea + Ornithine.
5. Compound X + Aspartic acid ____ Carbamylaspartate ____ Pyrimidines.

Figure 2

As may be noted, each time the cycle passes through the sequence of reactions, free ammonia is removed directly at Step 1 and indirectly via aspartic acid at Step 3.

Theoretically, according to Postulate 1, one might increase the capacity of the urea cycle for the removal of ammonia by the use of any of the substrate components of reactions 1 through 4. Greenstein et al.[2-6] in a series of experiments have shown that arginine is the most effective of the agents tested. Clinical use of arginine infusions in patients suffering from portal-systemic encephalopathy has been shown to produce most favorable results by Najarian and Harper[7] and as reported from this hospital by Manning and Delp.[8] The effectiveness of

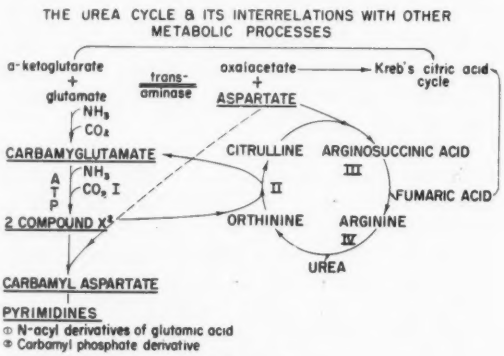

Figure 3

arginine as compared to the other possible substrates is probably because it more readily enters the hepatic cell.[1, 9] Also, the level of arginase in the liver is considerably higher than any of the other enzymes involved in the biosynthesis of urea.[10]

One other component of the urea cycle in mammals, carbamylglutamic acid, may also prove to be an efficient therapeutic agent. In experiments conducted by Dr. D. P. Wallach at the Upjohn Laboratories, carbamylglutamate acted efficiently in preventing ammonia intoxication, although not as well as arginine in acute experiments.[11] The effectiveness of this compound is limited by the fact that ornithine (the product of arginine therapy) has a much greater affinity for the enzymes of Step 2 than carbamylglutamate does for the enzymes of Step 1.[12, 15] Although this affinity has not been accurately measured, it is safe to say that it is at least 100 times greater as regards ornithine when compared to carbamylglutamate. Also the enzymes catalyzing Step 2 are present in mammalian tissues in concentrations at least 50 times those involved in Step 1.[12]

Besides acting as catalysts in the urea cycle, carbamylglutamic acid or the corresponding N-acyl (formyl, acetyl, etc.) glutamic acid derivatives are necessary in mammalian systems as active coenzymes for the biosynthesis of pyrimidines (reaction 5). Thus, the use of this compound in patients with liver disease might exert a two-fold effect on ammonia metabolism. It would promote the removal of ammonia via the urea cycle, and also might stimulate liver regeneration by its capacity to act as a coenzyme for the synthesis of pyrimidines and, therefore, of nucleic acids which are fundamental building blocks of the cell. It has been shown that the oral administration of carbamylglutamate results in an increase of enzymatic activity for citrulline synthesis.[16] For these reasons we are presently conducting clinical studies involving the prolonged oral administration of monopotassium carbamylglutamate to test its effectiveness in preventing the development of ammonia intoxication in susceptible individuals.

Acknowledgment

The author wishes to express his deep appreciation to Dr. Santiago Grisolia and Dr. Mahlon H. Delp for their stimulation and assistance in the preparation of this paper.

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All genuine progress results from finding new facts. No law can be passed to make an acre yield three hundred bushels. God has already established the laws. It is for us to discover them, and to learn the facts by which we can obey them.

—*Wheeler McMillen*

Hyperglobulinemic Purpura

Report of 14 Cases Fulfilling Waldenstrom's Criteria

SLOAN J. WILSON, M.D., *and* ROBERT E. BOLINGER, M.D., *with the technical assistance of* BETTY J. SLINKER, A. B., *Kansas City*

The concept of hyperglobulinemic purpura was introduced by Waldenström[1] in 1943. Three patients were described. A later article by the same author reported four additional cases.[2, 3] He further stated that he believed the disease or syndrome was not uncommon, of a benign nature, and of long duration. Twenty additional cases have been reported, 13 of which have been from the University of Kansas Medical Center.[4, 5, 6, 7, 8, 9, 10, 11, 12] Our previous report was of a preliminary nature, and it is our purpose now to present these patients in greater detail and add an additional case. We also believe that hyperglobulinemic purpura is much more common than is indicated in the literature.

Waldenström's criteria for the diagnosis of "purpura hyperglobulinemica" are as follows: The purpura is of a relapsing type, appearing chiefly on the legs, and occurs mainly after bodily exertion. There are no other signs of a hemorrhagic disease. The purpuric lesions are of short duration but are characteristic in that they leave pigmented spots on the legs. These have a typical appearance, thus making it easy to suspect the correct diagnosis.

There is an absence of any other "acceptable diagnosis." The serum globulin is increased, and there is no tendency for the protein increase to return to normal. The increase in protein is in the gamma globulin fraction. The erythrocyte sedimentation rate is accelerated. The usual coagulation studies are normal, including those of blood platelets. The course of the disease is benign, and the outcome has never been fatal.

All of our cases conformed to Waldenström's criteria, with the exception of two instances in which the platelet level was moderately decreased but not to hemorrhagic levels.

Methods

The electrophoresis of blood serum was done by the filter paper technique, using a modification of the method of Durrum,[13] Kunkel and Tiselius,[14] and Kunkel and Slater.[15] The addition of glycerol (5 per cent) was found to produce a more distinct pattern. Platelets were determined by the direct citrate method of Rees and Ecker[16] (normal 225,000 to 325,000 per cu. mm.). Prothrombin values were obtained by Quick's method.[17] Intravenous coagulation time was determined by the three-tube modification of the Lee and White method (normal 12 to 24 minutes).

Clinical Evaluation

The symptoms were consistent with those described initially by Waldenström. All but three patients were females. The principal reason for seeking medical assistance was the disfiguring pigmentation of the legs, as this was noticeable when sheer hosiery was worn.

Several patients noticed painful sharp needle-like sensations in their legs when fresh crops of purpura appeared. An excellent example was reported by a waitress who had no symptoms during the day, but if she went out dancing in the evening the purpura would be severe. Another patient, a

Fourteen cases of purpura with hyperglobulinemia are presented (purpura hyperglobulinemica of Waldenström).

The etiology is unknown. The disease or syndrome is of a benign nature. The purpura is of a recurrent type, confined for the most part to the lower extremities and associated with brown pigmentation of the skin.

Coagulation studies are normal. There is an abnormality in the serum proteins, with marked increase in the gamma globulin fraction.

Major surgical procedures were performed in two cases with no hemorrhagic tendency or increased loss of blood. Recovery was uneventful.

Various therapeutic regimens have had no effect. There was no benefit from corticotropin (ACTH) and corticosteroids.

From the Hematology and Metabolic Sections, Department of Medicine, University of Kansas Medical Center.

TABLE 1

CLINICAL AND COAGULATION DATA, 14 CASES OF HYPERGLOBULINEMIC PURPURA

Gamma Globulin Was Increased in Each Case

Pt.	*Age*	*Sex*	*Race*	*Duration of Disease*	*Gamma Globulin %*	*Total Protein gms. %*	*Platelets*	*Coagulation Time IV*	*Bl. time*	*Cl. retraction*	*Per Cent Prothrombin*
1.	41	F	W	5 yrs.	45	7.65	246,000	15′30″	1 min.	1½ hr.	87
2.	48	F	C	3 yrs.	26	7.8	246,000	20′30″	1′3″	....	....
3.	70	M	W	12 yrs.	22	5.6	264,000	12 min.	4 min.	4 hrs.	....
4.	23	F	W	2 yrs.	24	10.8	208,000	....	3′10″	2½ hrs.	....
5.	57	F	W	6 yrs.	48	10.2	255,000	18 min.	1 min.	2 hrs.	91
6.	27	F	W	5 yrs.	37	8.0	272,000	27min.	5′30″	1 hr.	71
7.	49	F	W	15 yrs.	38	9.0	165,000	19 min.	55″	2 hrs.	100
8.	35	M	W	2 yrs.	26	7.8	202,000	12 min.	2′15″	....	100
9.	42	F	W	7 mo.	45	8.25	170,000	15 min.	1′15″	1 hr.	82
10.	52	M	W	16 yrs.	22	7.8	165,000	9′30″	3 min.	....	90
11.	34	F	W	13 mo.	24	6.0	211,000	....	2′5″	....	....
12.	24	F	W	3 yrs.	28	7.5	402,000	16′30″	2′45″	1 hr.	100
13.	37	F	W	6 yrs.	32	8.1	85,000 114,000	17′30″	45″	3 hrs.	87
14.	33	F	W	5 yrs.	27	8.2	92,000 120,000	12 min.	3 min.	18 hrs.	76

nurse, developed purpura in the right arm in addition to purpura of the lower extremities. Further questioning revealed that she was a student health nurse, and the purpura was noticed particularly after she had shaken down thermometers when outpatients were numerous.

The duration of the purpura ranged from 7 months to 16 years (Table 1). There were three male patients and one Negro female in the group of 14. The age incidence was from 23 to 70 years. The earliest age at which purpura appeared was 21 years.

Examination revealed the typical purpuric and pigmented areas limited principally to the legs, with occasional similar lesions on the thighs. The recurring purpura resulted in a deposition of iron pigment in the skin. The presence of fresh purpura in the pigmented areas was striking. Enlarged hemorrhagic capillaries could be visualized by the use of clearing oil and a hand lens. Two patients had slight hepatomegaly. Liver biopsy was done in one case and a normal report was obtained. No other evidence of disease was found except in one patient, who had rheumatic heart disease with mitral stenosis.

Apparently the disease syndrome was benign in all patients.

Laboratory Observations

Coagulation studies (Table 1) included platelets, intravenous coagulation time, bleeding time, clot retraction, and prothrombin values. Platelet levels were excellent in all but two patients, and in these the platelet values were not in the hemorrhagic zone. All other tests were normal.

Particular attention was given to a study of the serum proteins. The gamma globulin peak was distinctly abnormal, being markedly elevated. Actual quantitative evaluation of the various protein components revealed that the gamma globulin ranged from 21 to 48 per cent of the total serum protein. (Normal average gamma globulin 12 per cent of the total serum protein.) The total protein is given in Table 1.

Evaluation of Possible Hemorrhagic Tendency

Coagulation studies reveal no defect in the coagulation mechanism. Not all known factors were evaluated. Two patients had been advised to have surgical procedures.

Patient No. 3, male, age 70 years, had benign prostatism with obstruction. Purpuric lesions had been severe for 12 years. A transurethral prostatic resection was accomplished with no excessive blood loss. The entire postoperative course was uneventful.

Patient No. 1, female, age 41 years, had rheumatic heart disease with mitral stenosis. Purpuric lesions had been noticed for five years. The Cardiovascular Service recommended that a commissurotomy be done. On the basis of our experience with the previous patient, we stated that excessive blood loss would probably not be a problem. Fortunately our prediction was true. A mitral commissurotomy was done without hemorrhage or postoperative bleeding. The recovery period was uneventful.

Evaluation of Therapy

Various therapeutic regimens have met with complete failure. Vitamins C and P had no effect. Antihistamines of various types were not beneficial.

None of the patients responded to intensive therapy with either corticotropin (ACTH) or corticosteroids. Figure 2 illustrates a patient treated with ACTH. The total amount of protein decreased, but the characteristic electrophoretic pattern of the serum proteins persisted. There was no clinical improvement.

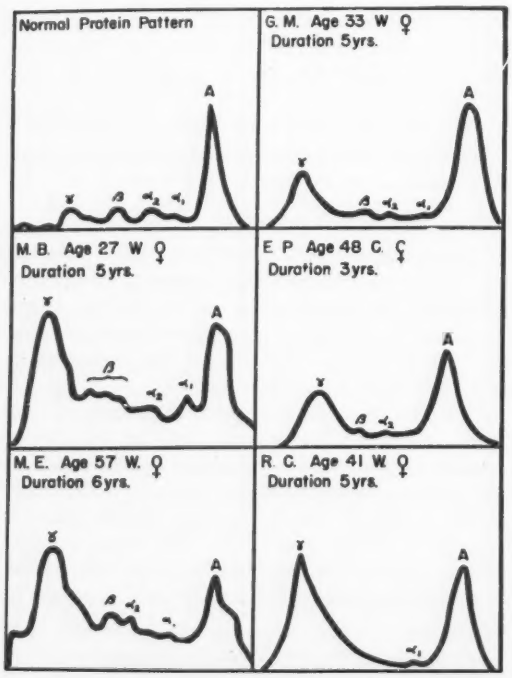

Figure 1. Serum protein electrophoretic pattern in purpura hyperglobulinemica (Waldenström). The upper left electrophoretic pattern is normal and can be used for comparison. The remaining five show an elevation in the gamma globulin peak.

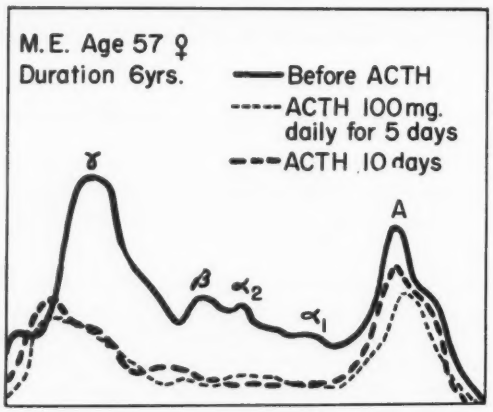

Figure 2. Effect of ACTH in a case of purpura hyperglobulinemica. Although the gamma globulin peak is decreased, the characteristic defect in the electrophoretic pattern remains.

Discussion

The 14 patients presented had essentially all of the characteristic features of hyperglobulinemic purpura as described by Waldenström.[3] To establish a diagnosis of this disease or syndrome it is necessary to eliminate systemic diseases that may be associated with elevated gamma globulin and purpura.

An elevated gamma globulin may be present in many diseases. Arends, Coonrad, and Rundles[18, 19] observed hypergammaglobulinemia in 6 of 10 patients with Hodgkin's disease and in 5 of 15 patients with malignant lymphomas and mycosis fungoides. In various types of leukemia an increase in globulin constituents frequently occurs. An increased gamma globulin may occur in lymphogranuloma inguinale, chronic liver disease, the collagenoses, sarcoidosis, and multiple myeloma.

Hemorrhagic tendencies associated with cryoglobulinemia or macroglobulinemia must be excluded. The clinical picture is entirely different. Cold worsens cryoglobulinemic purpura and is frequently associated with Raynaud's phenomenon. Purpura associated with large globulin molecules (macroglobulinemic purpura) usually occurs in elderly men with osteoporosis and generalized bleeding. Multiple myeloma may be present. The gamma globulin is not increased in idiopathic thrombocytopenic purpura.

The etiology of hyperglobulinemic purpura is unknown. No drugs or toxic agents have been incriminated in our cases or those reported in the literature. In our experience hyperglobulinemic purpura is not an unusually rare disease or syndrome. Waldenström also states that it is much more common than the lit-

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erature indicates. The statement of Seiden and Wurzel[12] is quoted herewith: "In conclusion, if there is such a syndrome as benign hyperglobulinemic purpura—that is, if the patients with known cases continue to enjoy good health despite purpura—the case presented—seems to fit the description—." The only contribution we can possibly make to this classic remark is to change "case presented" to "cases presented."

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Hyperthyroidism and Myasthenia Gravis

Case Report of Coincident Conditions

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In 1908 Rennie[1] reported the first case of hyperthyroidism and myasthenia gravis occurring together. Buzzard[25] in *Allbutt's System of Medicine* in 1910, writing about myasthenia gravis, stated that it frequently is associated with hyperthyroidism. Since that time there have been a number of reports of the two diseases occurring in the same patient. A review of the English literature reveals 85 fairly well documented cases have been reported.[1-24] Some of the reported cases are not included in this number, some being omitted because it was felt that the diagnosis was questionable.

Eaton[26] stated that 6 per cent of patients with myasthenia gravis at the Mayo Clinic either have or have had hyperthyroidism. At the Lahey Clinic 4.4 per cent of 90 patients with myasthenia gravis had hyperthyroidism,[16] and at the Johns Hopkins Hospital 5 per cent of 220 patients with myasthenia gravis had an "abnormality of the thyroid gland."[22] Kane[27] stated that approximately 24 reported cases of coincident hyperthyroidism and myasthenia gravis have been well documented.

It is felt that presentation of this case is justified because of the relatively few case reports of coincident hyperthyroidism and myasthenia gravis, and because this demonstrates the problem of differential diagnosis of muscle weakness accompanying hyperthyroidism.

A review of the English literature reveals that 85 fairly well documented cases of coincident hyperthyroidism and myasthenia gravis have been reported. An additional case is reported, the classification of muscle disorders occurring with thyroid disease is reviewed, and these syndromes are discussed.

From the Department of Internal Medicine, University of Kansas Medical Center. Dr. Shafer is a resident in internal medicine and Dr. Allen is associate professor of medicine.

Case Report

This 28-year-old white housewife was admitted to Kansas University Medical Center for the first time on October 29, 1955, with a chief complaint of goiter. She had been well until about three years before admission, when she began to have irregular menstrual periods, menorrhagia, and increasing nervousness. She was given iodine drops for a few months with subsequent improvement. Increasing enlargement of the thyroid with minimal dysphagia had first been observed two and one-half years before admission. Exophthalmos and diplopia of increasing severity began two years before admission. An increasing degree of nervousness and tremor had been present for one year, and at this time ptosis of the eyelids, which was more severe in the late part of the day, began.

In spite of a good appetite and adequate intake of food, the patient had lost weight from 140 pounds to 119 pounds in the year prior to admission. Weakness of the quadriceps muscles followed by generalized weakness had been present for four months, and for three weeks prior to admission she had been so short of breath and had such marked muscular weakness that she was unable to walk across the room. History of diarrhea, constipation, or abdominal pain was denied. Marked heat intolerance had been noted for an unknown period of time. She had been taking propylthiouracil for five months without improvement, and it had been discontinued one week before admission.

At the time of admission the patient appeared to be thin, apprehensive, and seriously ill. The blood pressure was 155/95 mm. Hg., pulse rate 152 per minute and regular, temperature 99.6 degrees Fahrenheit, respiratory rate 24 per minute, and weight 119 pounds. The skin was warm and moist, and there was a fine tremor of the hands. Obvious exophthalmos with a staring gaze and almost complete paresis of the extraocular muscles were present. The thyroid was diffusely enlarged, and a bruit was present over the gland. Depth of respiration was shallow, and the lungs were clear. The heart was enlarged to two centimeters to the left of the midclavicular line, and there were no cardiac murmurs or thrills. No organs or masses were palpable in the abdomen, and there was no tenderness. Actual muscular atrophy was not present, but marked generalized muscular weakness was apparent. Deep tendon reflexes were absent in the right extremities and sluggish in the left extremities.

Several urinalyses and complete blood counts were normal. Determinations of the blood urea nitrogen, fasting blood sugar, and serum electrolytes were within normal limits. Repeat determinations of 24-hour urinary excretion of electrolytes revealed that potassium excretion ranged from 52 to 192 milli-equivalents per 24 hours. X-ray of the chest was normal at the time of admission. Electrocardiograms were normal except for sinus tachycardia. Twenty-four-hour uptake of I^{131} was 56 per cent on October 29, 1955 and 61 per cent on December 8, 1955. Fluoroscopy of the chest and planograms of the superior anterior chest did not reveal enlargement of the thymus.

A diagnosis of thyrotoxic crisis was made on the basis of the history of goiter, weight loss, and heat intolerance; the physical findings of an extremely nervous and seriously ill woman, exophthalmos, goiter with a bruit, marked tachycardia, warm moist skin, and tremor; and an I^{131} uptake of 56 per cent in 24 hours. Accordingly the patient was given Lugol's solution four drops three times a day, sodium phenobarbital 120 milligrams intramuscularly every four hours, potassium chloride 4.0 grams a day, methimazole 10 milligrams every eight hours, and cortisone 100 milligrams orally every six hours.

When this patient was first seen it was felt that the muscular weakness was due to thyrotoxic myopathy; however, as the symptoms of thyrotoxicosis began to subside, as manifested by a decrease in the degree of nervousness and slowing of the heart rate, further observations made us question whether or not the patient might have some other disease in addition to hyperthyroidism.

Such weakness was present that she was unable to hold her arms above her body while in a supine position. Her vital capacity was decreased, and it was recorded as low as 800 mL. on several occasions. She stated that the muscular weakness was always worse in the late part of the day. During the second hospital week it was noticed that, after the patient talked for a short while, her voice became weak.

The possibility of the coexistence of myasthenia gravis and hyperthyroidism was considered. Because of this hypothesis, on November 18, 1955, the patient was given 0.25 milligrams of neostigmine methylsulfate intramuscularly, and it was observed that her muscular strength increased and her vital capacity increased from 800 to 1400 mL. On succeeding days 0.25 to 0.50 milligrams of neostigmine methylsulfate was given intramuscularly several times, following which there was increase in her muscular strength. On November 22, 1955, the administration of 15 milligrams of neostigmine bromide orally every eight hours was started. The dosage of neostigmine was progressively increased until she was receiving 15 milligrams every three hours from 6:00 a.m. to midnight. With this medication, remarkable increase of muscular power was observed. The degree of ptosis of the eyelids and weakness of the extraocular muscles was improved only slightly. Electromyographic studies performed before and after the administration of neostigmine gave results that were not typical of myasthenia gravis.

After the initial week in the hospital the dosage of cortisone and phenobarbital was decreased and, later, the administration of these drugs was discontinued. In the latter part of November, 1955, the administration of Lugol's solution and methimazole was discontinued. On December 8, 1955, the I^{131} uptake was 61 per cent in 24 hours, and the patient was given a therapeutic dose of eight millicuries of I^{131}.

After administration of the therapeutic dose of I^{131}, the patient's condition improved slowly, and intolerance to heat and muscular tremor decreased. By December 28, 1955, her weight had increased to 126 pounds, and her pulse rate was 100 per minute. Muscular power was improved as long as she was receiving neostigmine. She was discharged from the hospital December 31, 1955, with the only medication being neostigmine bromide 15 milligrams orally every three hours, 6:00 a.m. to midnight.

The patient was next seen February 3, 1956, at which time she was feeling much improved. She was spending much of the day up in a chair and was able to walk from the bedroom to the bathroom without assistance. At that time she weighed 127 pounds, her pulse rate was 94 per minute, and her hands were moderately warm. It was felt that she was still moderately hyperthyroid.

On April 2, 1956, it was observed that the patient's muscular power was much improved. She was up and around the house, doing the housework and the cooking. She was still taking neostigmine seven times a day. An I^{131} uptake was 46 per cent in 24 hours. Because it was felt that she was still hyperthyroid, 6.0 millicuries of I^{131} was given as a treatment dose.

By July 30, 1956, the patient was doing well. She was doing her own housework and, in addition to this, was able to walk across the street to a neighbor's house. The dosage of neostigmine had been decreased to 15 milligrams orally every four hours, 5:00 a.m. to 9:00 p.m. Examination revealed that the thyroid was no longer enlarged, the palms were neither warm nor moist, and there was no tremor. She had excellent muscular power, was able to hold her arms in any position, and was able to step up on a chair. There was no decrease in muscular power of her hands after repetitively gripping them 20 times. She was able to move her eyes 20 degrees laterally from a forward gaze. The I^{131} uptake was 17 per cent in 24 hours. It was felt that the patient was in a euthyroid state and that her myasthenia gravis was improved.

The patient was last seen November 13, 1956, at which time her condition was improved. She had reduced the dosage of neostigmine to 15 milligrams three times a day. She was able to perform all activities except that she did have some difficulty walking up and down stairs. She stated that she was improving as each month went by and that all muscular power was increased except that the degree of ptosis of the eyelids was slightly increased. Muscle power was normal except for a moderate degree of ptosis of the eyelids and limitation of lateral gaze to about 45 degrees. I^{131} uptake was 30 per cent in 24 hours, and the protein bound iodine was 5.8 gamma per cent.

Discussion

The syndrome of hyperthyroidism is familiar to all physicians. Likewise, it is well known that some weakness of the quadriceps femoris and ileopsoas muscles often accompanies hyperthyroidism. However, the fact that severe muscle disorders may accompany hyperthyroidism is not so well appreciated.

Several classifications of muscle disorders occurring with thyroid disease have been advanced. The classification most commonly quoted is that proposed by Starling, Drake, Hunt, and Brain[28] in 1938. A more useful classification is that given by Millikan and Haines.[21]

1. Thyrotoxicosis and
   - A. Myasthenia gravis
   - B. Chronic thyrotoxic myopathy
   - C. Periodic paralysis
   - D. Exophthalmic ophthalmoplegia
2. Hypothyroidism and altered muscle function

Exophthalmic ophthalmoplegia. Brain[29] wrote the classic article on this subject and popularized the term, but it has been discussed in other excellent articles.[14, 21] The syndrome consists of exophthalmos and ophthalmoplegia and implies only that these abnormalities may occur together.

It is a disorder localized in the soft tissues and muscles of the orbits. It may be due to an increase in the fat content of the retrobulbar tissues. Pathological examination of the extraocular muscles reveals that they are enlarged, edematous, and infiltrated with lymphocytes, connective tissue, and fat. This syndrome may be associated with any degree of hyperthyroidism and has been reported in patients in whom hyperthyroidism has not been recognized.

In this syndrome the weakness is limited to the extraocular muscles, and the levator oculi palpebrae are often spared. In minimal cases, the weakness may be limited to upward gaze. There is no characteristic fatigability of muscles as there is in myasthenia gravis, and the weakness is not improved by the administration of neostigmine. Usually there is chemosis, photophobia, and edema of the eyelids. The condition is most often bilateral but may be unilateral. Generally the ophthalmoplegia parallels the degree of exophthalmos, but there are exceptions.

Hyperthyroidism and periodic paralysis. The association of these two diseases is not common, but according to Millikan and Haines[21] is more common than would be expected by chance. They found that

in 400 cases of familial periodic paralysis reported in the literature, in somewhat less than 30 there was concurrent hyperthyroidism.

Familial periodic paralysis is characterized by periodic attacks of flaccid paralysis of muscles of all extremities. It has been noted that attacks are associated with low levels of serum potassium. Milhorat[30] stated that attacks can be terminated by the oral administration of potassium chloride, but other authors say that there is no immediate improvement by the intravenous infusion of potassium. With adequate treatment of the hyperthyroidism, attacks of periodic paralysis either disappear or become infrequent.

There should be no difficulty in differentiating this syndrome from the other muscle disorders that occur with hyperthyroidism. Patients with periodic paralysis are completely asymptomatic between attacks, and their muscles appear normal.

Chronic thyrotoxic myopathy. Some degree of muscle weakness, especially of the muscles of the legs, has been known for years to be part of the classic picture of hyperthyroidism. However, the full-blown picture of thyrotoxic myopathy is not widely known. This syndrome is characterized by muscle weakness and wasting. The etiology is not understood as with the previously described syndromes. It occurs in an older age group than does uncomplicated hyperthyroidism. The degree of muscle weakness and wasting is often greatly out of proportion to the degree of hyperthyroidism.

Muscles of the shoulder and hip girdles are most commonly affected, with those of the latter being the more severely involved. Smaller muscles are not usually affected, or at least not to the same degree, and muscle involvement is usually symmetrical. Muscles innervated by cranial nerves are not involved. Fasciculations have been reported by McEachern and Ross,[31] but in other cases they have not been seen.[14, 21] Tendon reflexes may be normal or symmetrically hyperactive. It is of interest, in the series of Millikan and Haines,[21] that 77 per cent of nine patients with chronic thyrotoxic myopathy were males and 80 per cent of 25 patients with hyperthyroidism and myasthenia gravis were females. Chronic thyrotoxic myopathy may present a picture similar to that of amyotrophic lateral sclerosis.

McEachern and Ross[31] reported that in their patients with chronic thyrotoxic myopathy there was some improvement of muscle power after the administration of neostigmine. However, most authorities agree that this does not occur in this group of patients. Muscle weakness and atrophy in chronic thyrotoxic myopathy are cured by adequate treatment of the hyperthyroidism.

Hyperthyroidism and myasthenia gravis. Myasthenia gravis is a chronic disease characterized by an increasing degree of weakness after the use of various voluntary muscles. Hyperthyroidism occurs more commonly in patients with myasthenia gravis than would be expected by chance.

Myasthenia gravis is due to a defect in neuromuscular transmission at the motor endplate, but the exact defect is not known. There is a close resemblance electromyographically between the neuromuscular block in myasthenia gravis and the block produced with d-tubocurarine in normal subjects.[32] Adams, Denny-Brown, and Pearson[33] stated that it is commonly assumed that defective production of acetylcholine at the motor end plate is the primary defect in myasthenia gravis. They concluded, however, that acetylocholine is only of relative importance in the pathogenesis of this disease and that the exact etiology is not understood.

In myasthenia gravis, characteristically, muscles innervated by cranial nerves are involved as well as muscles of the extremities. Patients often have ptosis of the eyelids and note an increasing degree of weakness as they talk, chew, or swallow.

There are no specific tests diagnostic of myasthenia gravis. The electromyograph may or may not be of value. Most important in making this diagnosis is some form of test using neostigmine, edrophonium, or curare.[35, 39] The neostigmine test may be performed in many ways. Tether proposed that 0.5 milligrams of neostigmine be given intravenously over a one-minute period. He stated that in myasthenia gravis there is improvement of muscle power before the needle is withdrawn. If side effects occur, atropine 0.6 milligrams is given subcutaneously.

Edrophonium is a drug similar in action to neostigmine but with a shorter duration. Because of this it is probably superior for testing for this disease. Ten milligrams of edrophonium chloride is injected intravenously, and, according to Osserman and Teng,[37] in patients with myasthenia gravis improvement in muscle power occurs within 30 to 40 seconds.

According to Millikan and Haines,[21] in some cases of myasthenia gravis there may be no improvement in muscle power after neostigmine administration, and in these cases the diagnosis may be established only by using some form of curare testing. One-tenth of the dose of curare that would produce mild curarization in a normal adult will produce aggravation of muscle weakness in a patient with myasthenia gravis. Much caution should be used in performing a curare test, however, as it is potentially a dangerous procedure. Individuals performing this test should be prepared to give artificial respiration and to give neostigmine or edrophonium intravenously if necessary.

Most authorities agree that improvement of muscle power after neostigmine administration does not occur in muscle disorders other than myasthenia gravis.

Millikan and Haines[21] stated that an increase or decrease in muscle power after neostigmine or curare administration respectively is diagnostic of this disease.

The reason for the association of these two diseases is not known. Kane[34] cited some interesting observations concerning the thyroid gland. He referred to work which revealed a significant increase in serum cholinesterase levels in 50 per cent of 35 patients with thyrotoxicosis, and to the common finding of focal collections of lymphocytes in voluntary muscles of patients with hyperthyroidism as well as those with myasthenia gravis.

Some observers have reported a "see-saw" relationship between these two diseases,[6, 15, 23] and they have noted that as the hyperthyroidism improved the myasthenia gravis became worse. Others have reported the opposite.[21] It is the opinion of these authors that the hyperthyroidism should, and as a matter of fact often must, be treated.

Hypothyroidism and altered muscle function. Part of the classical picture of hypothyroidism is the generalized slowing of muscle function. Means[40] stated that in patients with hypothyroidism muscles become weak and flabby and myalgias are often present. The decreased speed of contraction and relaxation of the gastrocnemius muscle in testing the Achilles reflex is characteristic of hypothyroidism.

Comments

The authors feel that the diagnosis of both hyperthyroidism and myasthenia gravis is well established in this case. The patient presented the classic history and physical findings of hyperthyroidism. The diagnosis of myasthenia gravis was established on the basis of the following findings. There was weakness of muscles innervated by cranial nerves, including extraocular muscles and those muscles concerned with speech, as well as weakness of the muscles of the shoulder and hip girdles and upper and lower extremities. There was weakness of the muscles concerned with ventilation, which does not occur in chronic thyrotoxic myopathy. There was increasing weakness of muscles with their continued use, which is pathognomonic of myasthenia gravis. Absence of typical electromyographic changes does not rule out this disease. Finally, marked improvement in muscle power after neostigmine administration is seen, according to most authorities, in no disease other than myasthenia gravis.

Several points deserve further comment. In this case, the myasthenia gravis became manifest after the first symptoms of hyperthyroidism appeared, and during thyrotoxic crisis. The so-called "see-saw" relationship between hyperthyroidism and myasthenia gravis is not seen for, as this patient became euthyroid, the myasthenia gravis steadily improved. Essentially all of the voluntary muscles of this patient were affected, and a striking feature was the reduced ventilatory capacity.

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Hemangioma of the Liver

Removal of Cavernous Tumor by Right Hepatectomy

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Although surgical removal of a part of the liver for tumor was successfully accomplished as early as the year 1891, the reported cases of total right hepatectomy are relatively few in number. Fineberg found only 20 cases reported in the surgical literature before March, 1955, and added a case of his own.[1] Only one of these cases had been reported prior to 1947. Four additional cases have been reported since March, 1955. The purpose of this article is to add another case of total excision of the right lobe of the liver for a cavernous hemangioma of massive proportions.

K.U.M.C. 54-6184, R. D. C., a 24-year-old white housewife, was admitted to the University of Kansas Medical Center on July 23, 1954, with the history of progressive abdominal enlargement for six years. Following a full term normal delivery of a 5 pound 13 ounce boy in 1948, her abdomen did not regress in size as expected. She had no other symptoms and successfully completed another pregnancy terminating in 1952 with the birth of a 4 pound 13 ounce girl. Although she remained asymptomatic, there had been a slow but continuous increase in the size of her abdomen. She continued her household duties, including the care of her two small children.

The patient had sought medical advice on several occasions for her progressive abdominal enlargement, and she had been informed that her liver was enlarged with displacement of her gallbladder to the left. No specific disease had been diagnosed. Other than iron therapy for anemia during pregnancy, she had received no treatment. Review of systems was negative except for some shortness of breath on climbing stairs. The past history and family history were not significant.

The patient was alert and cooperative and not in distress. Her height was 62 inches, weight 131½ pounds, blood pressure 148/80, and pulse rate 104 and regular. The heart was of normal size, and a non-transmitted systolic murmur was detected over its base. The upper abdomen was protuberant. A huge, smooth, firm non-tender mass could be palpated in the right upper quadrant. This was not separable from the liver. The mass extended to the left of the umbilicus and downward to the iliac crest. A one-millimeter, red, firm, non-tender nodule was present on the skin

The successful removal of a cavernous hemangioma involving the entire right lobe of the liver is reported. A detailed account of the surgical operation and postoperative course over a significant period is given. Experimental and clinical evidence indicates a more aggressive approach to hepatic tumors is justifiable.

From the Department of Surgery, University of Kansas Medical Center.

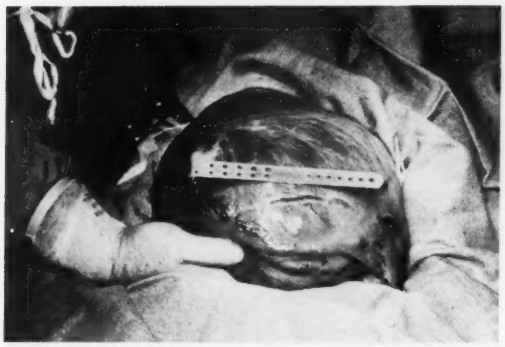

Figure 1. Photograph of the hemangioma taken at the operating table. The surgeon's hand rests under the inferior portion of the tumor, just above the right iliac crest.

over the dorsum of the right ring finger. There were no other significant findings.

Pertinent laboratory findings were as follows: red blood count 4,443,000, hemoglobin 10.0 gms., white blood count 9,700 with normal differential, urinalysis normal, sedimentation rate 25 mm. in 30 minutes, glucose tolerance (fasting and one hour intervals in sequence) 99, 89, 83, 75, 73, blood-urea-nitrogen 8.6, total protein 7.5 gms./100 cc., albumin 4.6 gms., globulin 2.9 gms., prothrombin time 75 per cent of normal, serum bilirubin direct 0.3 mgm. per cent, total 0.9 mgm. per cent. The bromsulfalein test showed all dye removed, the cholesterol was 304 mgm. per cent with esters 55 per cent of the total, alkaline phosphatase 2.1 Bodansky units, thymol turbidity 6, cephalin cholesterol 2 plus. The electrocardiogram was normal.

The chest roentgenogram was normal. Roentgenogram of the abdomen showed a homogeneous soft tissue density occupying the entire right side of the abdomen extending down to the pelvis. A cholografin study showed a gallbladder of normal size and shape displaced several centimeters to the left of the vertebral column. Intravenous pyelograms showed displacement of the right kidney to the left of the midline. An upper gastrointestinal series was normal except for displacement of the stomach and small bowel to the left.

The skin lesion on the right ring finger was excised under local anesthesia on July 27, 1954. Microscopic examination of paraffin sections showed focal acanthosis and hyperkeratosis with a few small capillaries in the upper corium.

The patient was transferred to the surgical service. Laparotomy was done on August 2, 1954, through a vertical right paramedian incision extending from the costal margin to below the umbilicus. The entire right side of the abdomen was found to be filled with a huge mass which replaced the right lobe of the liver (Figure 1). Many dilated pulsating vessels were present over the surface of the mass, which was nodular and firm in consistency. The right lobe of the liver was replaced by tumor except for a small margin along the falciform ligament. The left lobe was about three times normal size and was normal in color and texture. The caudate lobe was also free of involvement by the mass.

The incision was extended over the anterior course of the seventh rib, which was removed subperiosteally. The thorax was opened widely. The diaphragm was opened in a line parallel to its muscle fibers from the incision through the costal margin. This completely exposed the superior surface of the right lobe of the liver. The liver was then elevated through the incision through the diaphragm and permitting exposure of the porta hepatus.

The cystic duct was divided to enhance the exposure of the common hepatic duct. The right hepatic artery was greatly enlarged; it was estimated to be 18 mm. in diameter. It was ligated at its origin from the common hepatic artery and divided. The branch of the portal vein to the right lobe of the liver was ligated and divided. The right hepatic duct was divided, after a probe had been passed through the proximal end into the left hepatic duct for precise identification. The right lobe was then rotated anteriorly and medially to expose its posterior aspects.

The liver was dissected from the inferior vena cava. Numerous branches from the right lobe of the liver to the vena cava were divided between silk ligatures. In isolating the most superior vein, the vena cava was entered, requiring application of a non-crushing clamp for control. At this point excessive hemorrhage occurred from tears in other small branches to the inferior cava produced by traction on the mass. Non-crushing clamps were placed across the vena cava above and below the area. The liver substance was quickly divided between the right and left lobes, by successively placing large clamps across the parenchyma. Intercommunicating veins were individually clamped and ligated.

After the right lobe and tumor mass were removed, the bleeding points of the inferior vena cava were then sutured with 5-0 arterial silk. The cut surface of the liver was sutured with interrupted interlocking sutures of number 1 silk. The falciform ligament was sutured over a part of the transected surface. A T-tube was then placed with the short arms in the left hepatic duct and common duct, the long arm leading through the transected stump of the right hepatic duct and through the abdominal wall. Two large rubber-covered gauze drains were placed through a separate

stab wound from the transected surface of the liver and the right subphrenic area. The wound was closed in a routine manner without chest drainage.

A period of hypotension secondary to the bleeding from the vena cava when the mass was removed had existed for approximately 25 minutes. The systolic pressure varied from 60 to 30 mm. Hg. Otherwise the blood pressure and pulse were stable throughout the operation. Six thousand cc. of citrated blood were infused during the operation.

The patient was given 750 cc. of blood and 1000 cc. of dextran in addition to the other fluids during the first 48 hours postoperatively. Oral feedings were started on the fourth postoperative day; by the tenth day a high-protein high-carbohydrate diet was tolerated. A body temperature elevation occurred daily, reaching as much as 102 degrees Fahrenheit. A right pleural effusion occurred, and on the 22nd postoperative day 700 cc. of sero-sanguineous fluid was aspirated from the right pleural space. A few colonies of coagulase negative hemolytic staph aureus bacteria were grown from the fluid when it was cultured.

The patient was dismissed from the hospital on August 29, 1954, the 27th postoperative day, afebrile and free of symptoms. On October 4, 1954, she noted tenderness and swelling in the area of the incision on the right chest wall. There was a body temperature elevation to 100 degrees Fahrenheit. She was readmitted to the hospital on October 10, 1954. There was a tender fluctuant swelling in the scar of the thoracic portion of the incision and regional axillary adenopathy. An incision was made and the abscess was drained on the ward under local anesthesia. The wound was treated with irrigations of Dakin's solution. Purulent drainage ceased within 48 hours, and the swelling and tenderness subsided rapidly. Hemolytic staphylococcus aureus, coagulase positive, was grown on culture from the abscess. She was dismissed to her home on October 16, 1954, with a small residual clean granulating wound. Her last follow-up visit to the out patient clinic was on March 21, 1956, at

Figure 3. Photograph of the cut surface of the specimen. Note the large mottled dark areas, which represent blood-filled caverns. The intervening whitish tissue is somewhat dense and fibrotic.

Figure 2. Photograph of the specimen following removal. A rim of normal hepatic tissue is seen along the upper portion of the tumor, through which the transection was done. The gallbladder may be seen on the upper left part of the specimen.

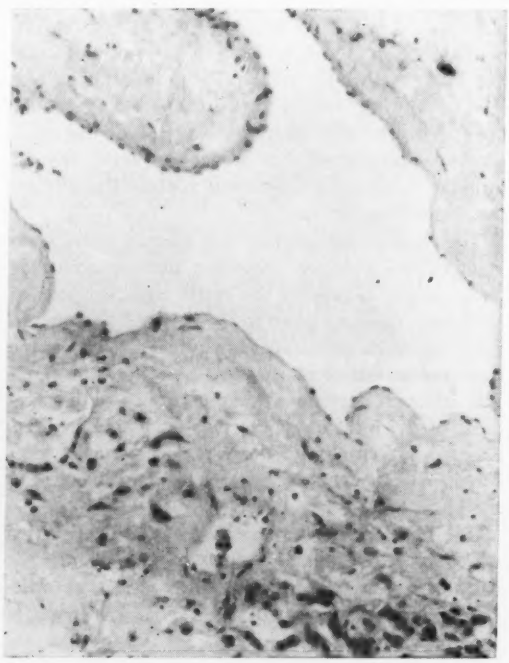

Figure 4. Photomicrograph of paraffin-fixed section from the tumor. See context for description. Note the distorted cords of liver cells in the lower portion of the field.

which time she felt well and was asymptomatic.

Liver function studies were done during the second (October, 1954) hospital admission. The bronsulphthalein retention test was negative, the cephalin cholesterol was negative, the thymol turbidity 10 units. The total protein was 7.60 gms. per cent, serum albumin 4.0 gms., serum globulin 3.6 gms. The serum bilirubin was direct 0.1 mgm. per cent, total 0.3 mgm. per cent, alkaline phosphatase 3.5, cholesterol 234. Cholesterol esters were 62 per cent. Roentgenograms of the intestinal tract following a barium swallow revealed the stomach to be shifted to the right, with the usual gas bubble resting under the right diaphragm. The stomach emptied normally.

The specimen weighed 6,500 grams and measured 29 x 24 x 10 cm. (Figure 2). It was of firm, rubbery consistency. Many large arborizing blood vessels were present over the surface of the tumor, measuring up to one cm. in width. The color was reddish-brown mottled with large blue areas. A rim of apparently normal hepatic tissue was present, measuring 8 to 9 cm. in width, extending along the entire length of the mass. A moderately distended greenish-colored gallbladder was present. On cut section, the mass was greenish-brown mottled with dark brown and reddish areas (Figure 3). A cystic space measuring 4 x 2.5 cm. was present, lined by a whitish glistening membrane and containing bright red blood. A second larger cyst was present containing a whitish gelatinous material. In another area measuring 2 x 0.8 x 1 cm., calcification was detected.

Microscopic examination of the tumor showed it to be made up of many large and small blood-containing spaces lined by a single layer of flat endothelial cells (Figure 4). Large intervening areas of fibrosis were seen with numerous brown pigment-laden macrophages. Distorted cords of liver cells exhibited degenerative changes and regeneration. Sections through the area of calcification revealed distinct bone formation (Figure 5). The pathologist's diagnosis was hemangioma of the right lobe of the liver; osseous metaplasia and focal fatty metamorphosis; miliary granuloma; and normal gallbladder.

Discussion

After reviewing the available literature we believe this to be the largest tumor of the liver to be successfully resected that has been reported. It is of interest to note that Pfannenstiel surgically removed a hemangioma of the liver weighing 5,290 grams, which was reported in 1898. Major and Black in 1918 reported a case of hemangioma of the liver weighing 18,160 grams.[3] This massive tumor caused the patient's death at the age of 36 years. No surgical treatment was attempted in this case.

Cavernous hemangioma of the liver is a benign tumor which may lead to the death of the patient. Upper abdominal trauma may rupture the highly vascular lesion with resultant fatal hemorrhage. Gradual enlargement may produce pressure on adjacent organs incompatible with life. Direct involvement of the liver parenchyma may produce hepatic insufficiency. Needle or direct biopsy of the lesion may be followed by severe hemorrhage. Complete surgical removal is the treatment most desirable, although remission of the growth has been reported following roentgen irradiation.[4]

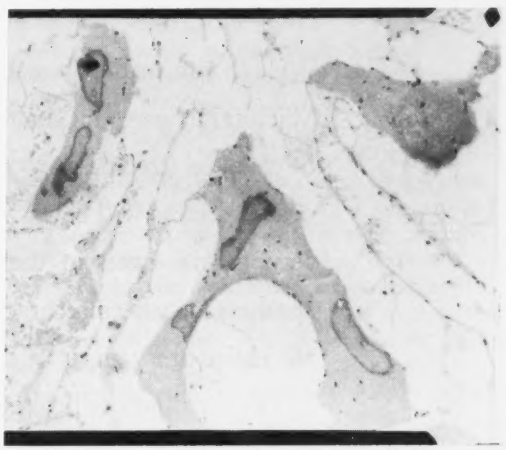

Figure 5. Photomicrograph of paraffin-fixed section from the tumor. Note the bone formation. The vascular nature of the tumor is clearly seen here, as denoted by the large spaces lined by flattened endothelial cells.

The regenerative capacity of the liver permits massive resections to be accomplished without demonstrable interference with liver functions.[2] The postoperative liver function studies in this instance actually showed diminution of the serum bilirubin to a normal range, and the patient's excellent postoperative health gives no indication of liver dysfunction.

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PRESIDENT'S PAGE

DEAR DOCTOR:

Have you made plans to attend the state meeting at Wichita? If not, you should. The meeting this year will be changed from past procedures. The first House of Delegates meeting will be Tuesday morning, and the scientific session will open in the afternoon. Several excellent speakers have been secured, and I am sure you will enjoy the entire program.

The Auxiliary will likewise be invited to the opening session, and I believe they too will enjoy these speakers. The Program Committee for this year has spent many hours planning for the 1957 meeting and as usual will give you something good as well as entertaining. The next issue of the JOURNAL will carry the official program.

It is my hope that each component society will be represented. This is your meeting and you are urged to attend, not only the scientific portion but the House of Delegates meetings as well. See your delegates at work.

Fraternally,

Clyde H. Miller M.D.

President

EDITORIAL COMMENT

School of Medicine Issue

The JOURNAL is bursting at the seams this month, packed with more good scientific material than has ever before been crammed into one issue, and the Editorial Board takes pleasure in giving credit where credit is due—to the University of Kansas School of Medicine. This is our 11th annual University of Kansas School of Medicine issue.

Dr. Vernon E. Wilson, assistant dean in charge of student affairs at the school, serves also as an associate editor of the JOURNAL, and his responsibility under the latter title is to assemble material for the March issue each year. The size, scope, and value of this 1957 issue attest to his success on the assignment.

Our thanks to Dr. Wilson, Dean W. Clarke Wescoe, and to all the others at the school who have made it possible for us to publish an exceptionally large issue on a variety of subjects of medical interest.

Proposed Practice Act

Two bills pertaining to the licensure of those engaged in the healing arts were introduced in the Kansas House of Representatives on February 18. House Bill 281 is a Basic Science Act and House Bill 282 creates a State Board of Healing Arts. A short story of events leading to the introduction of these bills follows, along with an analysis of their content.

Two years ago the House of Delegates of the Kansas Medical Society authorized the president to appoint a committee to draft a new practice act. On the committee are members of the Kansas State Board of Medical Registration and Examination and of the Kansas Medical Society. Also serving are the attorneys for each group.

The bills proposed by this committee were presented to the House of Delegates at a special meeting on October 28, 1956. They were approved, and the committee was then authorized to negotiate with the Kansas State Osteopathic Association and with the Kansas State Chiropractic Association and to amend the bills within the approved framework. Since that time the House of Delegates of the osteopathic organization has endorsed the proposed legislation and has agreed to support it in the legislature. The chiropractors are openly opposing both bills.

The proposed Basic Science Act will require each future doctor of medicine, doctor of osteopathy and chiropractor to demonstrate his knowledge of anatomy, physiology, chemistry, bacteriology and pathology before he may practice in Kansas. The board is to consist of persons holding doctorate degrees who are engaged in the field in which they will examine and shall be on the faculty of a state supported institution of higher learning in this state.

All persons now licensed in Kansas are exempt from this requirement. The examination for future graduates shall be written and certificates from other states with standards equal to those of Kansas will be honored.

It is *not* retroactive. The Basic Science Act involves only medicine, osteopathy, and chiropractic and no other profession. All others are specifically exempted. Only the healing arts are involved. Here is the definition: "For the purposes of this act, the healing arts include any system, treatment, operation, diagnosis, prescription, or practice for the ascertainment, cure, relief, palliation, adjustment, or correction of any human disease, ailment, deformity, or injury and includes specifically but not by way of limitation the practice of medicine and surgery; the practice of osteopathy; and the practice of chiropractic."

The Healing Arts Act creates a State Board of Healing Arts, consisting of five doctors of medicine, two doctors of osteopathy and two doctors of chiropractic who will sit as one unit on matters of policy, administration and enforcement.

The examination (with one exception described later) shall be given *only* by those members on the board who hold a license of the type sought by the applicant and no one may take the examination until he has obtained a certificate from the Board of Basic Science Examiners.

License privileges for medicine and for chiropractic in this act are identical with present provisions. The new act will create two classes of osteopaths.

The osteopathic "physician" has a license from the osteopathic members of the Board and may practice according to the interpretation of osteopathy by the Supreme Court of the State of Kansas.

The osteopathic "physician and surgeon" is an osteopath who was practicing in this state on January 1, 1957, or who graduated from an approved college of osteopathy after June 1, 1950, and who has successfully passed an examination in medicine and surgery given by the doctors of medicine on the Board. No other osteopathic physician is eligible to take this examination.

The medical profession agrees under terms of this act to conduct circuit course lectures for Kansas osteopathic physicians in those subjects upon which the examination will be given.

In other words, present physicians in each of the three branches of the Healing Arts are "grand-

fathered" in with exactly their present privileges and a way is provided for osteopaths who are now in Kansas, plus recent graduates, to increase their practice privileges.

Much more should be told about this long bill, but the above remarks contain the essentials. The purpose is best described by the bill itself as follows: "Section 1. Recognizing that the practice of the healing arts is a PRIVILEGE granted by legislative authority and is not a NATURAL RIGHT of individuals, it is deemed necessary as a matter of policy in the interests of public health, safety and welfare to provide laws and provisions covering the granting of that privilege and its subsequent use, control and regulation to the end that the public shall be properly protected against unprofessional, improper, unauthorized and unqualified practice of the healing arts and from unprofessional conduct by persons licensed to practice under this Act."

98th Annual Meeting

As enthusiasm mounts for the 98th annual meeting of the Kansas Medical Society, to be held at Wichita from Sunday, May 5, through Thursday, May 9, committees planning the event are completing final arrangements. The detailed program will not be announced until next month, but an outline of the schedule is now available.

PROGRAM. The formal program at the Wichita Forum will begin Tuesday afternoon. Two out-of-state speakers will be heard, after which two Kansas physicians will present papers having to do with the general subject of geriatrics. A scientific movie will start the program on Wednesday, and three guest speakers will give papers. After a round table luncheon at the Broadview Hotel, two panel discussions will be presented, one on cardiovascular diseases and the other on gastrointestinal diseases. The Thursday morning program will include a movie on a legal subject and three scientific papers.

BUSINESS. A change in format for this year's session provides that the first meeting of the House of Delegates will be held on Tuesday morning, beginning with a breakfast at 7:30 and closing by noon. The second meeting of the House will be held on Thursday afternoon, as in the past. Both will be at the Allis Hotel.

SPECIAL EVENTS. An innovation this year, the presentation of a television program from Chicago, over a closed circuit, will be a feature of the Monday afternoon program. A panel of psychiatrists in Chicago will interview a series of patients and discuss their findings with the audience over a two-way hook-up. A meeting of the Kansas Chapter of the American Academy of General Practice will be held Sunday afternoon and evening and Monday morning. Meetings of specialty societies will be scheduled to begin at 4:30 Tuesday afternoon, immediately after the close of the general session. Sports events are being planned for Monday with a sportsmen's banquet that evening.

BANQUET. The annual banquet of the Society will be held on Wednesday evening. During the program Dr. Clyde W. Miller will administer the oath of office to Dr. Barrett A. Nelson, president for 1957-1958. A dance will conclude the evening's events.

HOTEL RESERVATIONS. All hotel reservations are to be made individually. The largest hotels in Wichita are the Allis, the Broadview, and the Lassen.

Meeting of Pathologists

A joint meeting of members of the Kansas and Missouri Societies of Pathologists and of the College of American Pathologists in the southcentral region will be held at the Broadview Hotel, Wichita, on Saturday, March 30. A seminar on soft tissue and other tumors will be conducted by Dr. Richard Shuman, beginning at 9:00 o'clock. The moderator will be Capt. W. M. Silliphant, MC, U.S.N. After the banquet, Captain Silliphant will speak on aviation pathology.

Film on Crash Injuries

A 15-minute motion picture on the part being played by the medical profession in the prevention of auto crash injuries has been released jointly by the American Medical Association and the Ford Motor Company. Entitled "On Impact," the film is based on information about auto injuries presented at the A.M.A.'s annual meeting last June.

Prints of the film are being sent to all television stations in the United States for possible use on public service time. In addition, the feature can be booked from the A.M.A.'s film library by medical societies and their auxiliaries for showings at meetings or to the general public.

More than 396,000 health education pamphlets were sold by the American Medical Association's Bureau of Health Education during the 12 months ending June 30, 1956. The largest group sold, 69,000, concerned health of the school age child. Mental health pamphlets numbered 35,574, accidents and first aid 25,575, teeth 18,764, nutrition and diet 18,000, maternal health 17,296, physical fitness 15,319, and heart and circulation 12,400. Many of the pamphlets are reprinted from *Today's Health.*

Clinicopathological Conference

Intractable Heart Failure and Ammonia Intoxication

A 72-year-old white man complaining of shortness of breath and swelling of the ankles was admitted to the University of Kansas Medical Center for the second time on May 6, 1956.

He had been in fairly good health until September, 1955, when he began noticing weakness and fatigue. In December he had increasing dyspnea, orthopnea, and edema of the feet. His physician treated him with digitalis and diuretics, but he showed no improvement, and he was admitted to this hospital on March 7, 1956. At that time he had four plus pitting edema, rales in the bases of both lungs, Cheyne-Stokes respiration, and an enlarged heart with multiple murmurs. Treatment consisted of rest in bed, a low salt diet, digitoxin, aminophylline, and ammonium chloride. After two weeks he showed some improvement and had lost 23 pounds.

He was dismissed from the hospital on March 22 with instructions to continue to take digitoxin and aminophylline, but his symptoms again gradually increased, and he was readmitted on May 6 with severe orthopnea, edema, precordial pain, nausea, and vomiting.

He had had gonorrhea at the age of 21 years. In 1951 he was treated in our outpatient department for lues. His father and one brother had diabetes.

He was, at admission, a well-developed, well-nourished, chronically ill-appearing white man with Cheyne-Stokes respiration. His blood pressure was 135/50; pulse, 76; respiratory rate, 24. His pupils reacted to light and accommodation; there was arteriovenous nicking in the fundi. The upper respiratory examination was negative.

The neck veins were engorged, and moist rales were in the bases of both lungs. The apical cardiac impulse was in the sixth intercostal space at the mid-axillary line. The second aortic and second pulmonic sounds were poorly heard. There was a grade II diastolic thrill at the apex and a grade II systolic thrill in the second intercostal space at the right sternal border. A grade III systolic murmur was heard at the apex with a grade II presystolic crescendo murmur. A grade IV, harsh, systolic murmur was heard at the aortic area, and a grade III, aortic, diastolic murmur was transmitted to the apex.

The liver was firm and tender, and the edge was 8 cm. below the right costal margin. The tip of the spleen was palpable. There was three plus pitting edema of the lower extremities. Rhomberg's sign was positive, and the deep tendon reflexes of the lower extremities were absent. Babinski and Hoffman signs were absent.

The specific gravity of the admission urine specimen was 1.015; there was 2 plus albumin and 10 pus cells per high power field with pus clumps. The red count was 4,500,000 with 14 gm. hemoglobin, and the hematocrit was 42. The admission white count was 7,300 with 84 per cent polymorphonuclears. A subsequent white count on May 10 was 12,100 with 90 per cent filamented polymorphonuclears, 8 per cent lymphocytes and 2 per cent monocytes. On May 14, one day before death, the white count was 15,500 with 91 per cent polymorphonuclears, 8 per cent lymphocytes, and 1 per cent monocyte.

The serologic tests for syphilis were reactive with 32 Kolmer units and 4 Kahn units. The fasting blood sugar was 28 mg. per cent; sodium, 132 mEq/L; potassium, 6.1 mEq; chloride, 103 mEq; and carbon dioxide, 16.8 mEq. The blood ammonia was 163 gamma per cent; direct bilirubin, 2.6 mg. per cent; total bilirubin, 5.2 mg. per cent; thymol turbidity, 27 units; alkaline phosphatase, 3.5 millimol units; non-protein nitrogen, 99 mg. per cent. The blood urea nitrogen was 58 mg. per cent; creatinine, 2.5 mg. per cent. Subsequent blood sugar values ranged from 73 to 167 mg. per cent; subsequent blood ammonia from 145 to 225 gamma per cent.

On admission the patient appeared lethargic and slightly jaundiced. He was treated with intravenous fluids, digitoxin, aminophylline, vitamins, low salt diet, pentylenetetrazol (metrazol) and chlortetracycline (aureomycin). He was semicomatose most of the time, and could not be aroused. Numerous courses of monosodium glutamate were given with gratifying effect on the blood ammonia level which dropped from 225 to 148 gamma per cent.

In spite of therapy he rapidly became worse. On May 11 he developed muscular irritability and hyperactive reflexes. The blood pressure was 130/50; pulse, 112; respiration, 45; and the temperature

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Edited by Jesse D. Rising, M.D., and Mahlon Delp, M.D., from recordings of the conference participated in by the departments of medicine, pediatrics, surgery, radiology, and pathology of the University of Kansas Medical Center as well as by the third and fourth year classes of medical students.

was 101.4. On May 13 he was started on 50 mg. of cortisone daily. The next day a friction rub was heard over the precordium. His average urinary output was 800 milliliters per day, but dropped to 400 milliliters one day before death.

On the day of death the Cheyne-Stokes respiration was more pronounced; the blood pressure was 70/40; pulse, 120; blood urea nitrogen, 84 mg. per cent; creatinine, 3.0 mg. per cent; carbon dioxide, 28.5 mEq; and the blood ammonia was 145 gamma per cent. The total bilirubin was 19.1 mg. per cent; direct bilirubin, 11.8 mg. per cent; and the prothrombin time was 15 seconds.

On May 15, 1956, at 8:55 p.m. the patient suddenly died.

Dr. Mahlon Delp: Are there any questions of Dr. Kilk?

Richard D. Smith (fourth year medical student): I would like to know a little about his precordial pain.

Dr. Maert Kilk (resident in medicine): He had a sharp, precordial pain which was fairly severe when he was not comatose.

Norvin D. Schuman (fourth year medical student): Did the patient have a history of heart failure eight months previous to this?

Dr. Kilk: Not that I know of.

Ralph N. Sumner (fourth year medical student): Had he ever had rheumatic fever?

Dr. Kilk: Not to my knowledge.

Joseph Struzzo (fourth year medical student): Was there any evidence of embolic phenomena?

Dr. Kilk: No.

Mr. Sumner: Were blood cultures done?

Dr. Kilk: Yes; they were all negative.

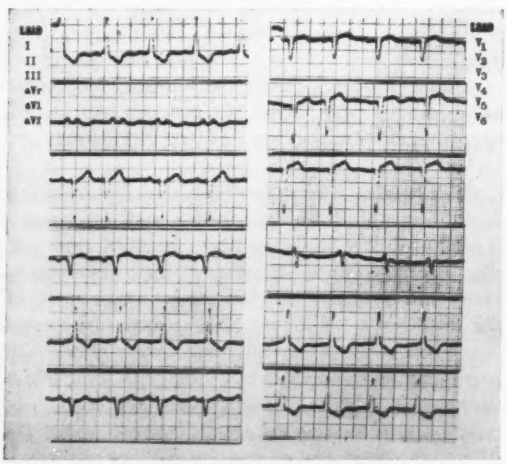

Figure 1. Electrocardiogram, March 7, 1956.

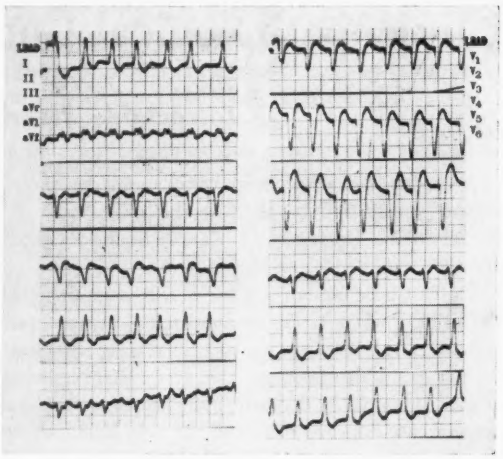

Figure 2. Electrocardiogram, May 12, 1956.

Gerald H. Siemsen (fourth year medical student): I would like to know more about his respiration.

Dr. Kilk: He had Cheyne-Stokes respiration, but he appeared quiet at the time of death.

Mack E. Sturgis (fourth year medical student): Did he have a falling blood pressure?

Dr. Delp: Yes, for several hours preceding his death, but the pulse rate remained about the same.

Mr. Siemsen: Was there cough or hemoptysis?

Dr. Kilk: No.

Mr. Sturgis: Was there a transaminase determination?

Dr. Kilk: The transaminase was 731 units.

Donald Stewart (fourth year medical student): What was the serum protein level?

Dr. Kilk: The serum proteins were: globulin, 3.2 mg. per cent; albumin, 3.7 mg. per cent.

Mr. Smith: Would you please review the neurological examination?

Dr. Delp: The neurological findings were equivocal, but I believe that there was no marked change in the reflexes in his lower extremities.

Mr. Siemsen: Can you be more specific about where the friction rub was heard?

Dr. Delp: Over the left precordium and the left chest.

Mr. Siemsen: Over a large area?

Dr. Delp: Over a rather large area. Mr. Sturgis, please demonstrate the electrocardiograms.

Mr. Sturgis: This tracing (Figure 1) was made on March 7. The rate is about 100 with a regular sinus rhythm. There is T-wave inversion in leads I, V5, and V6, and depression in the S-T segments. My interpretation is left ventricular hypertrophy and ischemia.

A second electrocardiogram, taken on May 12 (Fig-

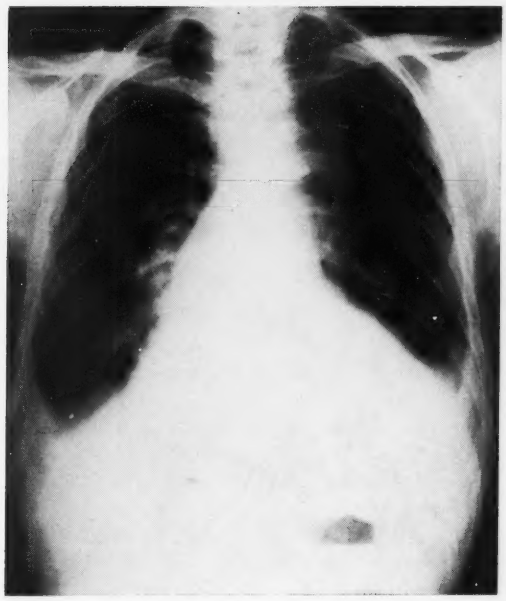

Figure 3. Chest film made on the sixth hospital day.

ure 2), shows tachycardia; I do not see a P-wave, so I interpret it as supraventricular tachycardia.

Dr. Delp: Mr. Stewart will now show the x-rays.

Mr. Stewart: The first is a chest film made on March 12, 1956 (Figure 3). There is no pathology in the bony structure, and no lung pathology except cloudiness in the right base, suggestive of congestion. The heart is considerably enlarged. The ascending aorta appears to be dilated. On March 20 there was clearing of the lung fields, but the heart was still greatly enlarged, and the ascending aorta still appeared to be dilated.

Dr. Delp: Mr. Schuman, let us have your discussion.

Differential Diagnosis

Mr. Schuman: I shall base my differential diagnosis on the causes of aortic valvular insufficiency with failure. First, I consider bacterial endocarditis; evidence in favor of this includes the heart murmur, the leukocytosis, and the patient's rapid deterioration. I rule it out because of the absence of anemia, embolic phenomena, and positive blood culture. My next consideration is syphilitic heart disease, the evidence for which includes postive serologic tests for syphilis, treatment for syphilis five years ago, aortic insufficiency, and signs of coronary insufficiency. Against this diagnosis are findings indicative of aortic stenosis, mitral stenosis (which one does not expect in pure luetic heart disease), and the description of the diastolic murmur which is not typical of pure syphilitic aortic insufficiency. Therefore, I rule out syphilitic heart disease.

Finally, I want to consider rheumatic heart disease. The findings are indicative of involvement of both aortic and mitral valves. This patient had findings of mitral stenosis with a rumbling presystolic murmur at the apex which may have been due to organic mitral stenosis. One can have a systolic, aortic murmur with syphilitic aortitis and dilation of the aorta, but that systolic murmur is usually of less intensity than the diastolic murmur. In our patient the opposite was the case. The findings at the apex, both the systolic and the diastolic murmur, can be explained on a functional basis. The murmur of functional mitral stenosis is not usually accompanied by thrill.

In review of the differential I must emphasize that I cannot rule out syphilitic heart disease or rheumatic heart disease, but, because the systolic findings are more prominent than the diastolic, I prefer the diagnosis of rheumatic calcific aortic stenosis and insufficiency. Calcific aortic stenosis is usually associated with rheumatic heart disease.

I think that this patient had rheumatic heart disease with a calcific aortic stenosis, aortic insufficiency, and mitral stenosis and insufficiency, probably on a functional basis. The congestion of the liver caused hepatic dysfunction, portal-caval shunting of blood and elevation of blood ammonia level, hyper-bilirubinemia and jaundice. It is also possible to have involvement of the kidney with renal tubular necrosis and uremia. I think the patient died in uremia with uremic pericarditis and depression of the central nervous system.

Clinical Discussion

Dr. Delp: Thank you very much for the discussion. Now I should like to know what you think of his chest pain. How do you explain it, Mr. Siemson?

Mr. Siemson: Uremic pericarditis.

Dr. Delp: Do you have a second possibility?

Mr. Siemson: Pulmonary insufficiency.

Mr. Sumner: It could have been from coronary insufficiency resulting from the calcific aortitis with occlusion of the ostia.

Dr. Delp: What about the elevation of the transaminase?

Mr. Struzzo: Myocardial infarction or liver damage.

Pathological Report

Dr. Frank Mantz (pathologist): The patient was considerably emaciated and cyanotic and showed edema of the lower extremities and distention of the cervical veins. There was 600 ml. of amber as-

citic fluid within the abdomen; 100 ml. of similar fluid within the pericardium; and 200 ml. within each of the pleural spaces.

The pertinent pathological changes were confined to the heart, lungs, liver, and brain. The heart was enlarged, weighing 810 gm., and showed a profound degree of hypertrophy of the left ventricle with a lesser degree of hypertrophy of the right ventricle. The myocardium showed no gross abnormalities. The epicardium was perfectly smooth, and nothing was found that would explain the friction rub that was heard clinically. The endocardium and valves, with the exception of the aortic valve, were normal except for uniform dilation of the valve rings. Major alteration of the aortic valve was noted. This consisted of a characteristic foreshortening and thickening of the cusps' margins (Figure 4). Associated with this, the left coronary orifice was displaced upward and completely out of the sinus of Valsava. More characteristic than anything else was the widening of the anterior commissure. Furthermore, there was a fusiform dilatation of the ascending aorta which we interpret as an early aneurysm. Associated with this is the "tree-barking" focal thickening of the intima characteristic of lues.

At the base of the aorta there was an inflammatory process characterized by a perivascular infiltration of lymphocytes and plasma cells within the adventitia, a feature practically pathognomonic of lues (Figure 5). This, apparently, was of long standing, producing patchy destruction of the elastica and fibrous replacement of the media, rendering the aorta more liable to dilatation and robbing it of its elastic recoil.

The disease of the aortic valve was not exclusively of luetic etiology. There was extensive calcification of the posterior cusps extending upward from the base of the valve itself and producing nodular protrusions (Figure 4). Furthermore, there was fusion of the posterior commissures, leaving the patient with an acquired bicuspid valve. In addition there was an extensive ulceration in the right posterior cusp suggestive of active subacute bacterial endocarditis.

Figure 4. Aortic valve and ascending aorta. Thickening of cusp margins is prominent, and the anterior commissure is widened. Note fusion of left posterior commissure, ulceration of right posterior cusp, and nodular calcification. The ascending aorta shows early aneurysmal dilatation.

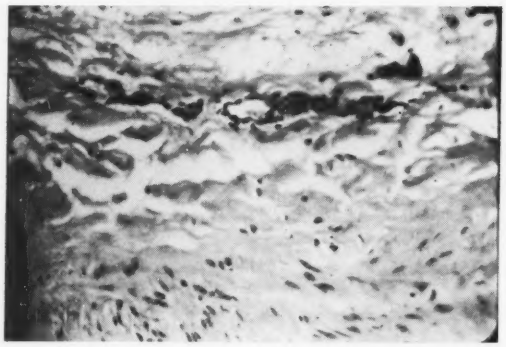

Figure 5. Aorta. Perivascular inflammation of vasa vasora in adventitia of aorta.

Histological examination confirmed the fact that calcific aortic stenosis did exist (Figure 6). The calcific deposit was confined to the valve ring and the central portion of the cusp in the area which is frequently referred to as the fibrosa. This change is characteristic of the rheumatic type of calcific aortic stenosis; the arteriosclerotic variety more frequently involves the spongiosa of the valve itself. Furthermore, there was extensive vascularization of the valve associated with residual inflammation likewise suggestive of rheumatic disease.

The area of ulceration did not prove, on histological examination, to be active bacterial endocarditis. It appeared to be a remote process, the nature of which we can only infer. There was a penetrating

Figure 6. Calcific aortic stenosis. Note deposition of calcium in fibrosa of cusp and extensive vascularity.

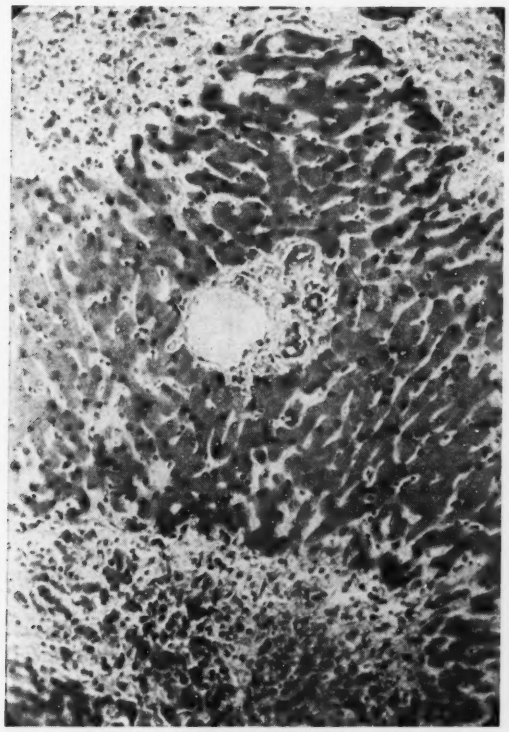

Figure 7. Liver. Marked central necrosis has reversed the usual relationship of the portal area with the central regions.

lesion extending deep into the fibrosa of the cusp and containing residual inflammatory cells showing a characteristic palisaded arrangement at the base of the lesion. It is our speculation that this represents healed sub-acute bacterial endocarditis, because of the characteristic inflammatory response. We have no way of proving or disproving this surmise.

For those who predicted that coronary insufficiency existed we can offer some support. There were areas of remote ischemia throughout the heart manifested by fibrous replacement. Examination of the coronary arteries failed to disclose any narrowing, and we must assume that the ischemia was on the basis of the malfunctioning aortic valve with myocardial hypertrophy.

The lungs weighed 1750 gm. and were exceedingly firm, exuding large amounts of frothy dark brown fluid. Scattered throughout the lower lobe on either side and also involving the lingula and the right middle lobe were focal areas of infarction of varying age and ranging from 5 to 9 cm. in circumference. The brown discoloration was caused by accumulation of hemosiderin-filled macrophages throughout the pulmonary parenchyma. Scattered throughout the pulmonary arteries were occasional small emboli of varying age which we assume were derived either from the right atrial appendage, which did contain a mural thrombus, or from the periprostatic veins which were thrombosed. We can infer that the relatively recent pulmonary infarcts contributed a hemolytic aspect to the patient's jaundice.

The liver showed advanced passive congestion, weighed 1500 gm., and showed characteristic rounding of the margins. The central areas were exceedingly prominent, retracted, and rather hemorrhagic. The portal areas were prominent and light yellow, suggesting a relatively high fat content. The architecture of the lobule was altered so that the relative prominence of the central and portal areas appeared reversed, a change characteristic of early passive congestion. Microscopically there was marked centrolobular necrosis. At the periphery there was considerable cloudy swelling with dissociation of the liver cords associated with narrowing of the sinusoids (Figure 7). Presumably this produced intralobular obstruction since the canaliculi were frequently distended with accumulated bile.

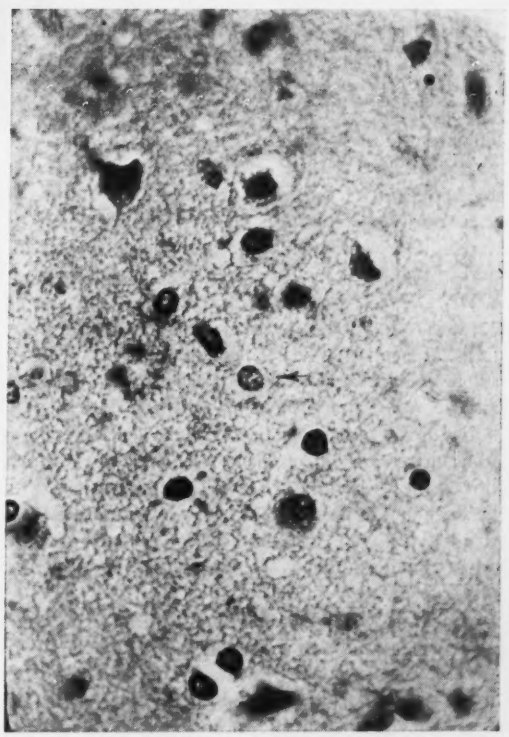

Figure 8. Brain. Note the large protoplasmic astrocytes of a type found frequently in hepatic coma.

The brain (Figure 8) likewise was of interest because of the history of anoxia, elevated blood ammonia and coma. There was evidence of generalized acute cell disease manifested by considerable chromatolysis, satellitosis, and alteration of Nissl's substances. There was also evidence that ammonia intoxication did exit in this case. Scattered throughout the brain, particularly within the diencephalon, there were astrocytes of a peculiar nature. These were large, with vesicular nuclei, and frequently showed an abundance of cytoplasm. Adams,[1] in his study of hepatic coma, found such cells to be present with a great degree of constancy. We believe this observation to be correct.

It is well known that luetic cardiovascular disease is frequently associated with involvement of the central nervous system. Such an association existed in this case. In addition to great atrophy, the cortex contained scattered rod-shaped microglia commonly found in luetic encephalitis. Furthermore, there were focal areas of glial proliferation beneath the ependyma of the fourth ventricle, producing a nodular alteration, often referred to as nodular ependymitis.

We believe that this man suffered from luetic aortic insufficiency and rheumatic aortic stenosis. The cardiac failure was engendered by this and led to passive congestion of the liver, resulting in hepatocellular degeneration and clinical impairment of hepatic function, including an elevated blood ammonia. As a result of this, and also as a result of anoxia, cerebral changes ensued. This case is interesting because it is the first one to be brought to my attention in which there was marked elevation of transaminase attributable to chronic passive congestion of the liver.

Dr. Delp: Dr. Allen, this patient, at the age of 72, was seen in the outpatient clinic, and the diagnosis of syphilitic heart disease was made. It was suggested that he should be treated with penicillin, and he was. Do you have any comments?

Dr. Max Allen (internist): There have been some discussions about the danger of treating syphilitic patients with narrowed coronary ostia with penicillin. The work done in our clinic disproves that danger. We have not experienced any trouble with penicillin therapy. There may be some danger with arsenic.

Dr. Delp: The fact that this patient had intractable heart failure is one of the strongest reasons for suggesting that he had syphilitic heart disease, but the character of his murmurs certainly makes this case resemble rheumatic heart disease. The other interesting thing is the elevation of his transaminase, and the fact that this patient did have ammonia intoxication with the neurologic complications that go along with that metabolic disturbance.

Pathological Anatomical Diagnosis

Primary

Luetic cardiovascular disease with fusiform aneurysm of the ascending aorta and aortic valvulitis.

Calcific aortic stenosis with fusion of posterior cusps consistent with healed rheumatic aortic valvulitis.

Focal ulceration of the right posterior cusp of the aortic valve consistent with healed subacute bacterial endocarditis.

Hypertrophy and dilatation of the left ventricle with focal myocardial fibrosis.

Organizing mural thrombi of both auricular appendages.

Nodular hyperplasia of the prostate and acute prostatitis, advanced, with thrombosis of periprostatic veins.

Acute and chronic passive congestion of the lungs.

Multiple small, relatively remote and recent emboli in pulmonary arteries with multiple hemorrhagic infarcts of the lungs.

Sanguineous pleural effusions: 200 ml., right; 600 ml., left.

Dilatation and hypertrophy of right ventricle.

Acute and chronic passive congestion of the liver with central necrosis, advanced.

Chromatolysis, satellitosis, hyperplasia of large pale astrocytes and edema of brain with perivascular hemorrhages consistent with ammonia intoxication.

Generalized jaundice, advanced.

Acute and chronic passive congestion of the spleen, kidneys and gastrointestinal tract, advanced.

Ascites, 600 cc., and peripheral edema, moderate.

Inactive luetic encephalitis.

Summary

Dr. Delp: A most resistive form of congestive failure was, as is often true, complicated by metabolic failure and ammonia intoxication terminally. This central nervous system intoxication is not an uncommon end result of liver damage coming on with severe congestive hepatomegaly.[2]

Preventive treatment of the heart lesion with penicillin late in the patient's life was certain to fail, and was made more surely so here by the presence of coexisting rheumatic valvular disease.

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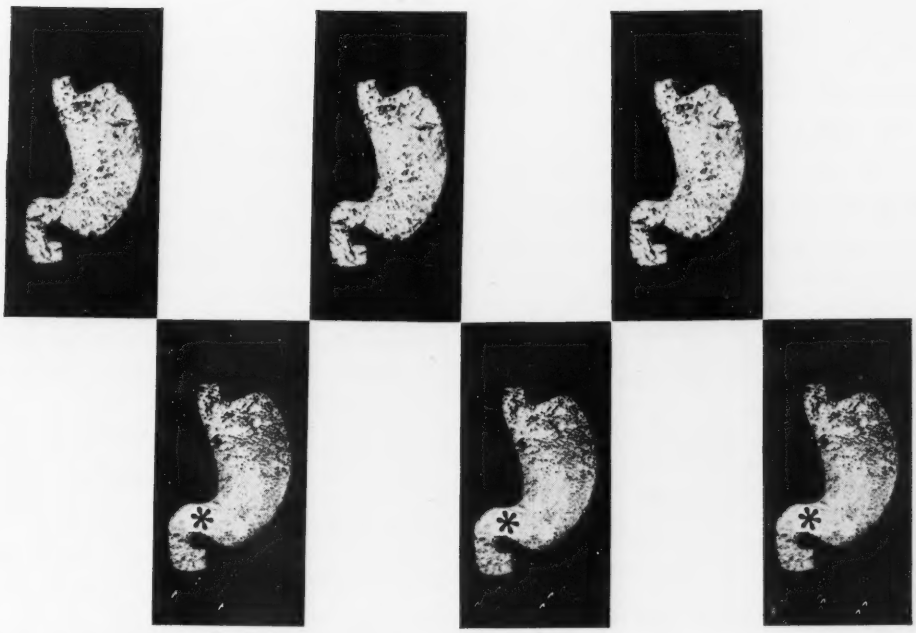
TRUE ANTICHOLINERGIC ACTION



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The therapeutic action of Pro-Banthine in decreasing hypermotility and hyperacidity, together with the remarkable early subjective benefit, is a desired approach in the management of ulcers.

The initial suggested dosage is one tablet, 15 mg., with meals and two tablets at bedtime. An increased dosage may be necessary for severe manifestations and then two or more tablets four times a day may be indicated. G. D. Searle & Co., Chicago 80, Illinois, Research in the Service of Medicine.

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BLUE SHIELD

What Makes Blue Shield Different?

One frequently hears doctors ask, "Isn't Blue Shield just 'another insurance company'?" This question usually comes from a member of the generation of new doctors who have come into practice since the early '40's, and who know little of the desperate challenge that gave rise to the Blue Shield idea and the hard work with which its accoucheurs gave it birth.

Blue Shield represents a vast and triumphant effort on the part of American medicine to prove to the people of the United States that, with their help, their doctors can solve urgent problems of medical economics without governmental interference or dictation. Blue Shield was created at a time when the insurance industry questioned the actuarial feasibility of voluntary medical care insurance on any large scale, and even many doctors feared that a voluntary program would inevitably lead to a compulsory health insurance system under government auspices.

Blue Shield has little in common with commercial accident and health insurance beyond the fact that it utilizes actuarial principles. Where the insurance company underwrites selected groups to produce a profit, Blue Shield, reflecting the service ideals of the medical profession, makes its services available to the entire community, at rates based on the needs and experience of the community—including most particularly those people in the low income groups who need medical prepayment protection.

Where commercial insurance companies offer cash allowances which may or may not have any relation to the doctor's normal charge for his services, Blue Shield's schedules of payment are negotiated and approved by the local medical profession. In most areas Blue Shield benefits take the form of fully paid professional services, through the cooperation of the "participating physicians." Even where "service benefits" are not provided by formal agreement of the doctors, plan schedules generally attempt to approximate the normal charges of local physicians for services rendered people in the lower income brackets, and local physicians frequently accept these fees as full payment.

Blue Shield Plans are distinguished by non-profit operation, which means that their only purpose is service to the people and their doctors. Non-profit operation also means that all funds contributed by subscribers are available for payment of benefits, with a minimum retained for actual operating costs and reserves for future claims.

Over and above all requirements of state law, Blue Shield Plans are required to maintain strict "membership standards" in order to use the name and symbol "Blue Shield." These standards provide that the plan must have the continuous approval of the local medical society; must render an annual report to the society; and must secure the formal participation of at least 51 per cent of all physicians in the plan area. In Kansas, 95 per cent of the medical doctors (nearly 1,800) are Blue Shield participating physicians.

Blue Shield utilizes insurance principles, but, because of the participation of the great majority of American physicians, it is able to transcend the limits of insurance—to become a true community service on behalf of America's physicians.

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HENRY EDGAR HASKINS, M.D.

Dr. H. E. Haskins, 78, who was in his 55th year of medical practice, died at Kingman Memorial Hospital on February 1, two days after having suffered a heart attack. A graduate of Beaumont Hospital Medical College, St. Louis, in 1901, Dr. Haskins returned to Kansas immediately to start practice in Kingman in association with his father. The two later founded the Kingman Memorial Hospital.

Recognition for 50 years of practice was given by the Kingman community in May of 1952, and further recognition was given the following year when Dr. Haskins represented Kansas at the first Western Hemisphere Conference of the World Medical Association at Richmond, Virginia.

Dr. Haskins held many offices in his county and state medical societies and was also a member of the Kansas State Board of Medical Registration and Examination for a number of years.

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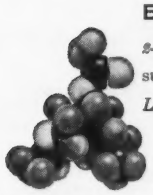

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Maternal Hypofibrinogenemia

A Study of Coagulation Defects in Pregnancy

ROBERT N. SMITH, M.D., ***Panama Canal Zone***

Hemorrhage is among the leading causes of maternal death in the United States. During the last few years it has become evident that certain instances of hemorrhage during pregnancy have been associated with disturbances in the blood clotting mechanism.

DeLee[1] was called in 1901 to attend a case of abruptio placentae with uncontrollable hemorrhage. He made the observation that the patient's blood failed to clot even after several days and described the condition as a "temporary hemophilia."

Willson[24] in 1922 reviewed a number of cases associated with bleeding phenomena and attributed these to the liberation of a hemorrhagic toxin by the placenta.

The nature of this hemorrhagic phenomenon was not investigated systematically until recently. The first demonstration of the nature of the defect was made in 1936 by Dieckmann,[2] who found significantly reduced levels of blood fibrinogen in patients who suffered hemorrhage following abruptio placentae.

It must be realized that knowledge of this subject is in its beginning stages. One should be cautious in accepting generalizations drawn from the few carefully observed cases which have been reported.

Mechanism of Coagulation

Though it is not within the scope and purpose of this paper to go into the intricacies of blood coagulation, a short discussion of its mechanism is relevant. It is still evident after many years of study and research that the entire mechanism of blood coagulation is not fully understood. Therefore a simplified concept will be given to the reader, and no attempt will be made to go into the controversies of the subject.

Thrombin is an enzyme which acts on blood fibrinogen, a soluble protein, to convert it to fibrin, an insoluble protein. This is probably a polymerization reaction. The fibrinogen molecules form needle-shaped protofibrils which become aligned into fiber strands. They are extremely adhesive and possess the capacity to contract. This reaction takes place in about nine minutes in a normal blood sample. Fibrinogen is a globulin with a molecular weight of ca. 410,000. The molecule is three or four times as large as other plasma proteins.[5, 15]

Thrombin, normally not present in blood, has its origin in prothrombin. Prothrombin is present in the circulating blood in a concentration of about 20 mgm. per 100 cc. Prothrombin is activated by calcium, thromboplastin, Ac-globulin, platelet derivatives, and possibly some substances that are not recognized as yet.[15]

Thromboplastin is widely distributed in the body as an intracellular substance, particularly in the lungs, brain, and kidney in the nonpregnant animal. It is present to a much greater degree in the placenta and decidua of the pregnant animal.[14]

Accelerator globulin is one of the newly recognized clotting factors. It acts together with thromboplastin and calcium to activate prothrombin rapidly.[7, 15] The mode of action by which Ac-globulin accelerates the conversion of prothrombin to thrombin is unknown.

It is known that the platelets furnish an agent which accelerates the interaction of thrombin and fibrinogen.[25] The platelets also contain an accelerator which catalyzes the change of prothrombin to thrombin by thromboplastin and calcium ions.

The fluidity of the blood is maintained by the balance between the system for prothrombin activation and the system of inhibitors of prothrombin activation. One of the inhibitors is heparin which interferes with the action of thrombin on fibrinogen.

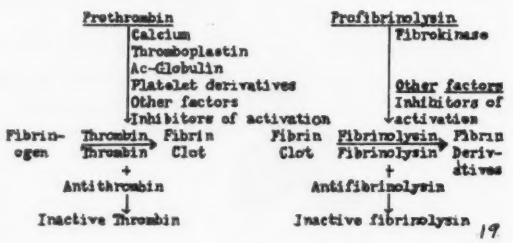

Figure 1

This is one of 11 theses, written by fourth year students at the University of Kansas School of Medicine, selected for publication by the Editorial Board from a group judged to be the best by the faculty at the school. Dr. Smith is now serving his internship at Gorgas Hospital, Panama Canal Zone.

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Another is antithromboplastin which is believed to inactivate thromboplastin. A number of other anticoagulant factors have been studied, but their character is obscure.[15]

Human plasma also contains a potent proteolytic enzyme capable of dissolving a clot. This enzyme fibrinolysin (plasmin) is ordinarily in an inactive form, profibrinolysin (plasminogen), a protein normally found in the plasma. It can be activated by fibrokinase, of tissue origin, and perhaps by other physiological mechanisms. Plasma is not only potentially fibrinolytic but also has strong plasmin-inhibiting activity, antifibrinolysin (antiplasmin), which can destroy the activity of the fibrinolysin itself.[15, 25]

Average Fibrinogen Values

Peterman[9] states that the fibrinogen content of blood plasma remains fairly constant in the normal non-pregnant individual, being stabilized somewhere between 250 and 350 mgm. per cent. The average fibrinogen level of normal non-pregnant women is 260 mgm. per cent, according to Dieckmann.[3] In normal pregnancy there is an increase to an average of 480 mgm. per cent at term with a further increase during the first postpartum week. There is an average increase in plasma fibrinogen of about 40 per cent at term.

In eclampsia the blood fibrinogen level becomes high with an average of 660 mgm. per cent at term. In preeclampsia the average fibrinogen concentration at term is 510 mgm. per cent.

Hemorrhagic States in Pregnancy

Under a variety of conditions associated with pregnancy and occurring at or near the time of parturition, a more or less transitory abnormality sometimes appears in the clotting mechanism which may be responsible for uterine and generalized bleeding. These syndromes include premature separation of the normally implanted placenta, amniotic-fluid embolism, retention of a dead fetus in utero, hydatidiform mole, eclampsia, and severe preeclampsia. It also has been observed to occur following criminal abortion and lung surgery.[11]

Experimental Studies

Weiner and his associates[23] advanced three possible explanations to account for the hypofibrinogenemia they observed. One possible explanation was that a toxic placental or fetal substance was depressing the production of fibrinogen by the liver. They believed this unlikely since hepatic function was normal in their patients. Ratnoff et al.[10] noted that fibrinogen given to the patient intravenously disappeared within a few hours. This cannot be explained on the basis of this theory.

The second hypothesis proposed by Weiner and his coworkers[23] was that circulating fibrinogen may be removed by excessive plasma proteolytic activity. However, various investigators have not been able to establish the presence of an active fibrinolysin in this condition with any degree of consistency. Also the concomitant reduction of prothrombin and Ac-globulin as well as fibrinogen cannot be explained by the action of fibrinolysin.[5] The existence of fibrin emboli and retroplacental clots is further evidence against this mechanism.

The third hypothesis proposed by Weiner et al.[23] was that clotting had occurred intravascularly. The data presented make this seem to be a reasonable hypothesis.

The problem was first studied by injecting tissue extracts into experimental animals intravascularly. The material used was simple, crude, saline extract of various tissues. Schneider[14] was able to show that the active principle was actually tissue thromboplastin. He theorized that since heparin blocks the blood clotting mechanism by blocking the activation of prothrombin, i.e., by blocking the formation of thrombin from prothrombin under the influence of thromboplastin, heparin should provide protection against placental toxin. This was found to be the case in vivo experiments. He found that he could produce intravascular coagulation by injecting thromboplastin. He also found that he could protect these animals by giving heparin intravenously either before or with the thromboplastin. These findings are in agreement with those of Thomas.[21]

The basic lesion produced in those animals that die at once is microscopic and characteristic. It may be described as a disseminated thrombo-embolism of the pulmonary arterial vasculature.[15] The structure of these thrombo-emboli indicates that fibrin elements have been deposited by increments under tension from the flowing arterial circulation. The filaments of fibrin are oriented with the longitudinal axis of the vessels. There are few erythrocytes but relatively many leucocytes enmeshed in these thrombo-emboli.[8] These characteristic fibrin structures have been observed in different parts of the greater circulation, especially in the brain.

The experimental lesions described above appear to be the result of intravascular fibrin formation. However, animals that survive a sublethal dose of thromboplastin may develop one or more complications from the resultant depletion of fibrinogen. First, there is a lack of response to further injection of thromboplastin. Fulton and Page[5] have shown not only that animals in this state of resistance are markedly deficient in fibrinogen, but that sensitivity to the thromboplastin extracts could be restored by

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artificially replenishing the plasma fibrinogen. Similarly the sensitivity returns upon natural replenishment of the fibrinogen by the animal's own liver.

In these animals the injection of thromboplastin has caused an intravascular defibrination.

Schneider[15] also found it possible to cause pregnant animals to develop numerous difficulties by traumatizing the placenta. To perform this experiment, he made abdominal incisions and traumatized the placentas of pregnant rabbits by repeated manual compression through the intact uterine wall until complete placental separation had taken place. There was evidence that the active agent was thromboplastin, and its source was the maternal placenta. Death resulted from disseminated pulmonary thrombo-embolus. Trapped within these thrombo-emboli were formed elements derived from the maternal portion of the placenta. Among the surviving rabbits there were also perivascular hemorrhage and local necrosis within the brain. There was liver necrosis which was comparable microscopically and grossly with that following thromboplastin injection. Schneider[15] was able to induce the release of thromboplastin from a vulnerable portion of the conceptus into the maternal circulation.

Let us turn now to the human. Schneider[16] believes he has evidence leading to the conclusion that thromboplastin does gain access to the maternal circulation in human pregnancy.

Almost any tissue or body fluid may serve as a source of thromboplastin.

TABLE I

QUANTITY OF THROMBOPLASTIN OBTAINED FROM VARIOUS TISSUES

Source material	*Thromboplastin Units per gram of tissue* *
Amniotic fluid	1
Liver	10
Skeletal muscle	20
Kidney	50
Brain	50
Lung	200
Placenta	
First trimester	2000
Term	200
Decidua	
First trimester	2000
Term	1500

* One unit of thromboplastin is the minimum lethal dose required to kill a 20-gram mouse.

Table I shows that the placenta is rich in thromboplastin, especially early in pregnancy. The decidua is unusually rich and remains so even at term. The amount of this potent material in these tissues, plus their anatomic relation to the maternal circulation, demands that one consider that thromboplastin from these tissues can get directly into the maternal circulation.

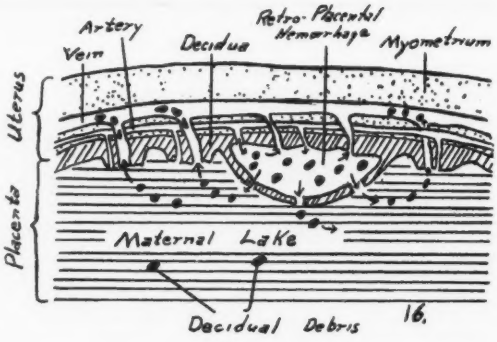


Figure 2

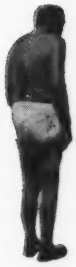
Figure 2 presents a hypothetical mechanism through which this might occur. A spontaneous hemorrhage into the degenerating decidua mixes maternal blood with decidual debris and tissue juices, all rich in thromboplastin. This mixture could then escape through breaks in the fragile basal plate into the maternal or intervillous lake of the placenta. From there the mixture could gain entrance to the general maternal circulation. Complications may result, including "fibrin embolism" because of initiation of coagulation within the circulating blood.

Schneider[16] found and described two retroplacental hematomas, each still in situ on its delivered placenta. One was a self-limiting retroplacental hematoma from a case of eclampsia, the other an extensive hematoma from a case of clinically diagnosed abruptio placentae. Each case demonstrated partial defibrination clinically. Study of microscopic sections revealed lacerations of the basal plate in both placentas. It was inferred that at the time of rupture of the basal plate, a thromboplastic mixture escaped into the maternal lake and then into the maternal circulation.

Detection of Hypofibrinogenemia

A rapid, quantitative test to determine the value of the plasma fibrinogen is of prime importance to the clinician. Unfortunately patients for whom this test would be desirable do not always present themselves to the physician during the hours when the services of the laboratory technician are readily available. Therefore the physician himself should become familiar with a method of detecting defibrination.

Weiner et al.[22] advocated the "clot observation test." This test is done by observing the stability of



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In correlating serial fibrinogen values with clot stability it appears that blood containing approximately 150 mgm. fibrinogen per 100 cc. of plasma serves as the dividing line between clot stability and clot instability. When the approximate fibrinogen range per 100 cc. of plasma varies between 150 mgm. and 100 mgm., partial clot dissolution with separation of red cells is evident. Soft fragile clots formed which promptly dissolved between 100 mgm. and 60 mgm. per 100 cc. of plasma. Blood containing less than 60 mgm. fibrinogen per 100 cc. of plasma fails to clot.[6]

Between the values 250 mgm. and 150 mgm. per 100 cc. of plasma, fibrinogen depression occurs without recognizable clinical symptoms to justify the designation "sub-clinical" defibrination. Below 150 mgm. per 100 cc. of plasma, fibrinogen depression is accompanied by symptoms characteristic of the "clinical" disease. Below the critical level of 100 mgm. to 90 mgm. per 100 cc. of plasma, complete failure of the coagulation mechanism becomes evident. This may be characterized by generalized hemorrhagic symptoms such as epistaxis, hematuria, melena, gingival bleeding, and bleeding at the sites of venipunctures.[6, 11]

Abruptio Placentae Syndrome

In the abruptio placentae syndrome the degree of defibrination is directly proportional to the severity of placental abruption. Schneider's[16] opinion that the defibrination may be selflimited when resulting from abruptio placentae was confirmed by Hodgkinson et al.[6] He was also able to demonstrate by serial fibrinogen studies that placental abruption preceded fibrinogen depression. The defibrination was generally progressive as long as the abruptio process continued. Termination of pregnancy abruptly reversed the downward trend.

If, as it appears from the foregoing statements that the underlying pathologic process is a progressive one, beginning with intravascular coagulation and proceeding essentially to defibrination, it follows that the appropriate treatment might be quite the opposite during the two phases of this continuous process. During the coagulative phase, the use of anticoagulants may conceivably be appropriate to prevent or reduce complications that might be anticipated to result from disseminated fibrin deposition. If this were to be attempted, due precautions should be taken as regards both mother and fetus.[14, 17]

By contrast, if the patient were to be first seen after the coagulative process had essentially reached completion, the desirable treatment would be the prompt replacement of blood loss and institution of measures to combat shock. Secondly she should be given an intravenous injection of at least two to six grams of purified human fibrinogen in an attempt to reestablish blood fibrinogen concentration to normal values. If fibrinogen is not available, fresh whole blood may be used. However, Weiner et al. state that for each pint of blood with a fibrinogen level of 250 mgm. per cent, the effective increase would only be about 10 mgm. per 100 cc. of plasma. One good alternative is the use of quadruple strength small pool plasma. One pint yields 4.4 grams of fibrinogen.[6, 11]

Next, measures should be taken to empty the uterus. If the cervix is not long and closed, and amniotomy can be performed readily, this procedure should be carried out. However, if labor does not follow promptly, if it is difficult to keep the patient out of shock, or if laboratory studies show that fibrinogen depletion is continuing at a rapid rate, it is probably in the best interest of the patient to empty the uterus promptly by cesarean section. No surgical procedure should be attempted, however, without first restoring the blood coagulation mechanism.[6, 11]

Amniotic Fluid Embolism

Steiner and Lushbaugh[20] first described amniotic fluid embolism in 1941. The amniotic fluid enters the maternal circulation just before, during, or shortly after childbirth. In about two-thirds of the reported cases, the women have been 30 years of age or older, and most have been multiparous. In at least half the cases labor has been excessively severe and rapid. Typically, severe respiratory distress with dyspnea and cyanosis suddenly develops and the patient dies within a matter of minutes. If the patient survives the initial shock of amniotic fluid embolism, there is usually gross uterine hemorrhage which does not always respond to supportive measures. At autopsy, evidence of embolization of the maternal circulation by amniotic fluid is present; lanugo hairs and desquamated fetal epithelium can be found in the mother's pulmonary vessels.[6]

In amniotic fluid embolism it is not clear whether intravascular coagulation or fibrinolysis is the major etiological factor. Reid et al.[13] claim that amniotic fluid embolism induces intravascular coagulation. The low thromboplastin activity of amniotic fluid and the delivery of intact ovisacs, in a certain number of cases with hypofibrinogenemia, speak against this theory. It appears reasonable also to assume that amniotic fluid embolism leads to shock and consequent fibrinolysis.[12]

Treatment consists of the measures outlined in the abruptio placentae syndrome: replacement of blood

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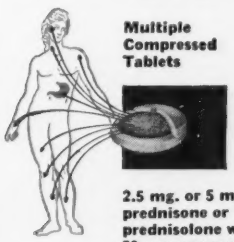

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References: 1. Boland, E. W., *J.A.M.A.* 160:613 (February 25) 1956. 2. Margolis, H. M. *et al.*, *J.A.M.A.* 158:454 (June 11) 1955. 3. Bollet, A. J. *et al.*, *J.A.M.A.* 158:459 (June 11) 1955.

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loss, administration of two to six grams of fibrinogen intravenously, and rapid digitalization. Amniotomy should be carried out if possible, but other surgical procedures are probably contraindicated.

If the patient should exhibit signs of obstetric shock but no blood loss, one should be cautious about rapid intravenous infusions of either blood or fluids. The patient's already embarrassed pulmonary circulation makes her a likely candidate for pulmonary edema with possibly a fatal consequence.

Intrauterine Retention of Fetus

A third cause of hypofibrinogenemia in pregnancy is the intrauterine retention of a dead fetus. When the "dead fetus syndrome" was first described by Weiner et al.,[23] it was suggested that maternal-fetal Rh incompatibility was an essential etiologic feature. Later it was found that the Rh factor was only of apparent etiologic importance, and its relationship to the syndrome was incidental to the increased frequency with which intrauterine death occurred in maternal-Rh isoimmunization. Hypofibrinogenemia has not been reported in cases in which fetal death occurred earlier than the fourth month of gestation, nor has hypofibrinogenemia been noted in less than five weeks after the apparent death of the fetus.[10]

Mechanisms responsible for the hypofibrinogenemia are not known. One hypothesis suggested is that the maternal fibrinogen is destroyed as the result of fibrinolysis. If fibrinolysis were the only abnormality, one would not expect a concomitant drop of fibrinogen, prothrombin, and Ac-globulin, which can be marked at times.

A more plausible explanation for hypofibrinogenemia is that the fibrinogen is consumed by intravascular coagulation. This view is supported by the observation that intravenously injected fibrinogen disappears from the circulation with great rapidity.[10, 12] Perhaps thromboplastin material, from the placenta, the dead fetus, or the amniotic fluid, gains entrance to the maternal circulation. No evidence has been reported that decreased synthesis of fibrinogen is responsible for the hypofibrinogenemia.

A change in the traditional attitude of "watchful expectancy" in the management of missed abortion and dead fetus in utero may well be overdue. Prophylactically, patients in whom there is retention of a dead fetus should be warned to report any evidence of bleeding, however trivial. Determination of the fibrinogen concentration should be started in the third week after fetal death and should be repeated at weekly intervals. It is probable that the "hands off" policy should be followed as long as weekly plasma fibrinogen values range above 150 mgm. per 100 cc. of plasma. In the range between 90 and 150 mgm. per 100 cc., the frequency of serial blood sampling should be increased to several times daily, and preparations should be made for delivery.[6, 11]

The method and time for interruption of pregnancy in the "dead fetus syndrome" depend upon obstetric conditions. A long, hard, undilated cervix is probably sufficient indication for hysterotomy.[12] If the condition of the cervix is favorable for delivery, amniotomy is probably a wise procedure. Emptying the uterus, after intravenous injection of human fibrinogen, corrects the defect promptly.

Summary

In some patients with abruptio placentae or amniotic-fluid embolism, hypofibrinogenemia may develop acutely and may be associated with both uterine and generalized bleeding. The cause of the hemorrhagic phenomena in these two conditions is unknown. It is conjectured that thromboplastic material enters the maternal circulation and causes introvascular coagulation, with subsequent defibrination. Treatment in both disorders should include intravenous injection of human fibrinogen and measures to combat shock. In abruptio placentae the uterus should be emptied, preferably by vaginal delivery. In amniotic-fluid embolism conservative management has been more effective.

A third cause of hypofibrinogenemia in pregnancy is the intrauterine retention of a dead fetus. In these cases fetal death usually occurs in the fourth month of gestation or later, and hypofibrinogenemia has been noted five or more weeks thereafter. The mechanism responsible for hypofibrinogenemia is unknown. These patients should be studied frequently for evidence of bleeding or hypofibrinogenemia. Emptying of the uterus after intravenous injection of human fibrinogen corrects the defect promptly.

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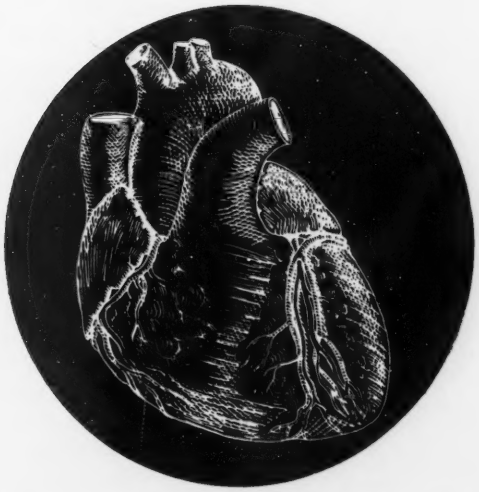

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COUNTY SOCIETIES

Dr. Samuel Zelman, Topeka, spoke on "Liver Function Tests—A Clinical Evaluation" at a meeting of the Shawnee County Society held on February 4. At the business session Dr. H. H. Woods was elected to honorary membership and Dr. A. G. Stutz was elected to active membership.

"Lymphomas in Childhood" was the subject discussed by Dr. William G. Klingberg, St. Louis, at a meeting of the Sedgwick County Society on February 5. Speaker at the next meeting, on March 5, was Dr. Francis M. Ingersoll, Boston, who spoke on "Polycystic Ovarian Syndrome and Indicated Surgery."

Members of the Wyandotte County Society entertained their wives and office assistants at a dinner meeting at the Town House Hotel, Kansas City, on February 19.

Members of the Auxiliary were guests of the Cowley County Medical Society at a dinner held at the Winfield Country Club recently. Dr. Glen Floyd later addressed the physicians' group on the subject of "Diseases of the Eye."

Dr. and Mrs. Roswell E. Capsey, Centralia, entertained members of the Nemaha County Society and its Auxiliary at a buffet supper at their home recently. During a separate scientific meeting which followed, the physicians saw a film on cancer prepared by the Upjohn Company and presented by an Upjohn representative, Mr. Del Saunders.

Officers of the Smith County Society were elected at a meeting held at Smith Center recently. Dr. Frank H. Relihan is now serving as president, Dr. Hugh J. Woods as vice-president, Dr. Victor E. Watts as secretary-treasurer, and Dr. Dennis A. Hardman as delegate to the state meeting.

A meeting of the Leavenworth County Society was held at Leavenworth on February 11. Members made plans for a number of public relations and public service projects, polio immunization, 24-hour telephone service, and formation of a grievance committee.

An engraved gold watch was presented to Dr. Eugene J. Bribach, Atchison, at a recent meeting of the Atchison County Society. The occasion was Dr. Bribach's anniversary of entering the practice of medicine, his 50th. Dr. Frederick Wrightman, Sabetha, councilor for that district of the Kansas Medical Society, addressed the group.

A remarkable increase in cancer deaths since the beginning of the 20th century is shown in the statistical tables of the World Health Organization. Among many possible causes of this rise, the aging of the population should be mentioned. Furthermore, in the past 50 years other causes of death such as the infectious diseases have lost much of their importance, thus increasing the proportion of some other conditions as cause of death.

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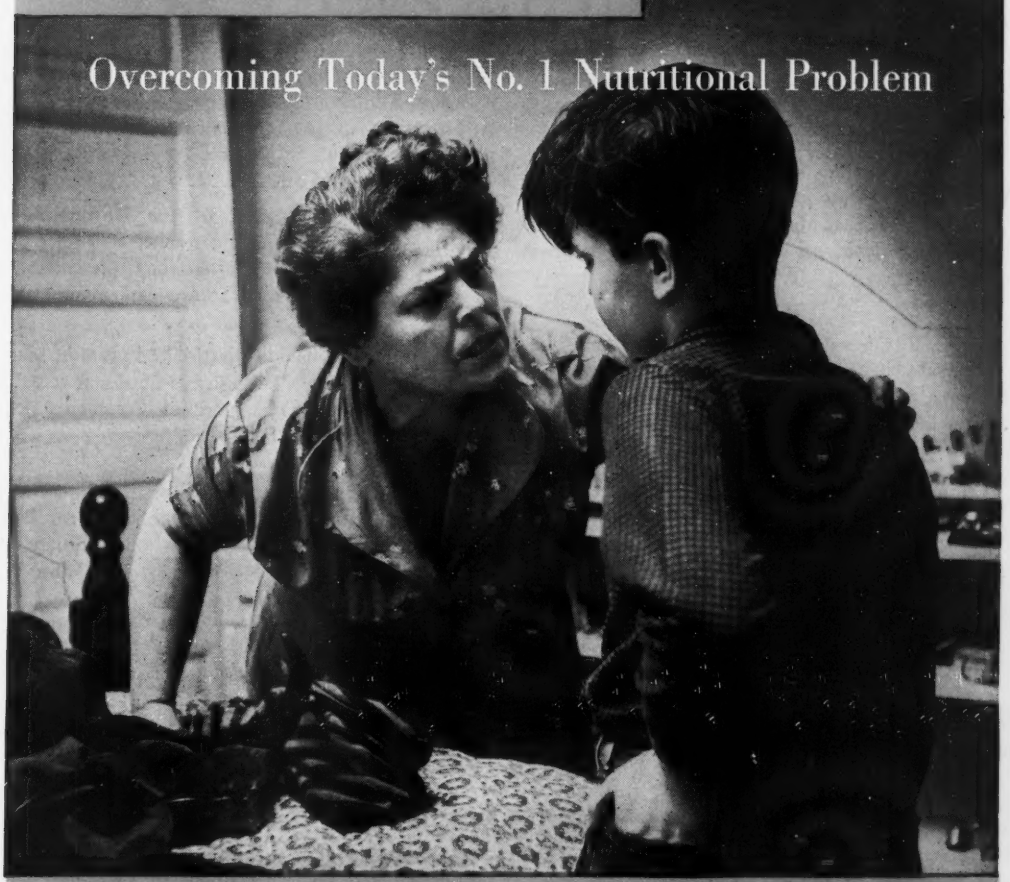

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PHYSICIANS' ACTIVITIES

Dr. Condon T. Hagan, Wichita, addressed a district meeting of medical technologists in Wichita recently on the subject of "Heart Catheterization."

After a six months' sabbatical leave in Europe and Asia, **Dr. E. Grey Dimond** has returned to the University of Kansas Medical Center where he is professor of medicine and chairman of the department of medicine.

Dr. C. R. Openshaw, who served at the Hutchinson Naval Air Station during a term of duty with the Navy, has returned to Kansas to practice surgery in Hutchinson. A graduate of the University of Utah, Dr. Openshaw had a three-year fellowship in surgery at the Mayo Foundation, followed by a two-year fellowship in thoracic surgery.

The Marshall County Board of County Commissioners has named **Dr. George I. Thacher,** Waterville, county health officer.

Dr. Herbert Modlin, lecturer in psychiatry at the University of Kansas Medical Center, went to Cincinnati last month to address the Industrial Management Club on "Psychiatry in Industry."

The Mentor Study Club at Hillsboro held an open meeting recently at which **Dr. Herman F. Janzen,** Hillsboro, was speaker. He discussed "Prevention and Treatment of Heart Conditions."

Dr. Charles C. Coady, Kansas City, retired as medical director of the Buick-Oldsmobile-Pontiac assembly plant in Kansas City on February 1. **Dr. Harold Y. Allen,** who had been on the plant's medical staff since last April, took over the duties of director.

"Criteria for Satisfactory Colectomy for Carcinoma of the Left Colon with Description of Early High Ligation of the Inferior Mesenteric Vein" was the subject discussed by **Dr. Stanley R. Friesen,** of the University of Kansas Medical Center, when he spoke before the Central Surgical Association at a meeting in Chicago on February 21.

Dr. Daniel V. Conwell and **Dr. C. J. Kurth,** Wichita, were speakers at a meeting held in Arkansas City on February 6 under sponsorship of the Cowley County Association for Mental Health. Dr. Conwell discussed "Everyday Care of Mental Patients," and Dr. Kurth spoke on "Proper Management of Mental Cases."

Dr. Eugene J. Bribach, Atchison, was guest of honor at a dinner at the Bellevue Country Club, Atchison, on January 22, in recognition of his completion of 50 years of practice.

Dr. Leroy A. Calkins, of the University of Kansas Medical Center, was a speaker at a refresher course in obstetrics and gynecology presented at the University of North Carolina last month.

Recognition for having practiced 54 years in Manhattan was given **Dr. William H. Clarkson** recently when the Manhattan Chamber of Commerce held its annual dinner.

Dr. Forrest L. Loveland, Topeka, resigned his position as plant physician for the Goodyear Tire and Rubber Company of Kansas on February 1. He was succeeded in the position by **Dr. John W. Cavanaugh.**

Dr. Z. Miles Nason, Kansas City, was speaker at a recent meeting of the Kansas City Ministerial Alliance. He discussed the work on the Kansas State Commission on Alcoholism.

An office for the practice of surgery has been opened in Pittsburg by **Dr. John G. Esch,** former staff surgeon at the VA Hospital in Johnson City, Tennessee. Dr. Esch, a graduate of Creighton University School of Medicine in 1948, completed a three-year fellowship in surgery at Cleveland Clinic before entering practice.

Dr. Benjamin H. Mayer, Ellsworth, has announced his retirement from practice, effective last month.

The University of Tennessee is the largest of the 76 approved four-year medical schools in the country on the basis of total enrollment. A recent report by the American Medical Association shows that, during the 1955-1956 academic year, five medical schools had a total enrollment of more than 600 each. The University of Tennessee had 781 students. It was followed by the University of Michigan with 762, Jefferson at Philadelphia with 677, the University of Illinois with 636, and the University of Texas at Galveston with 614.

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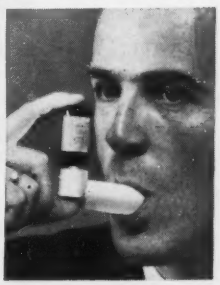

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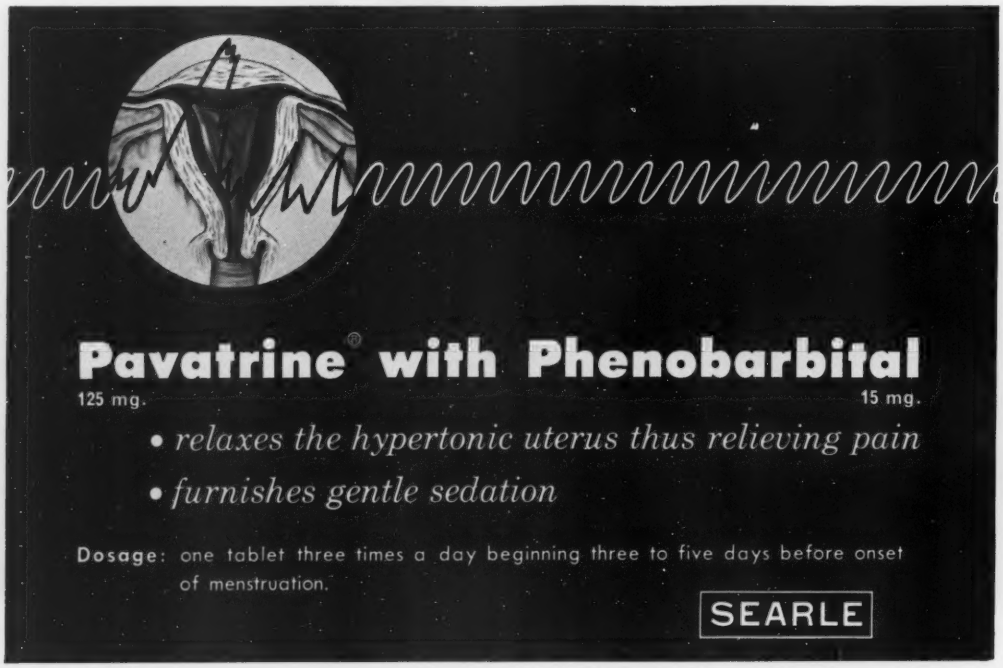
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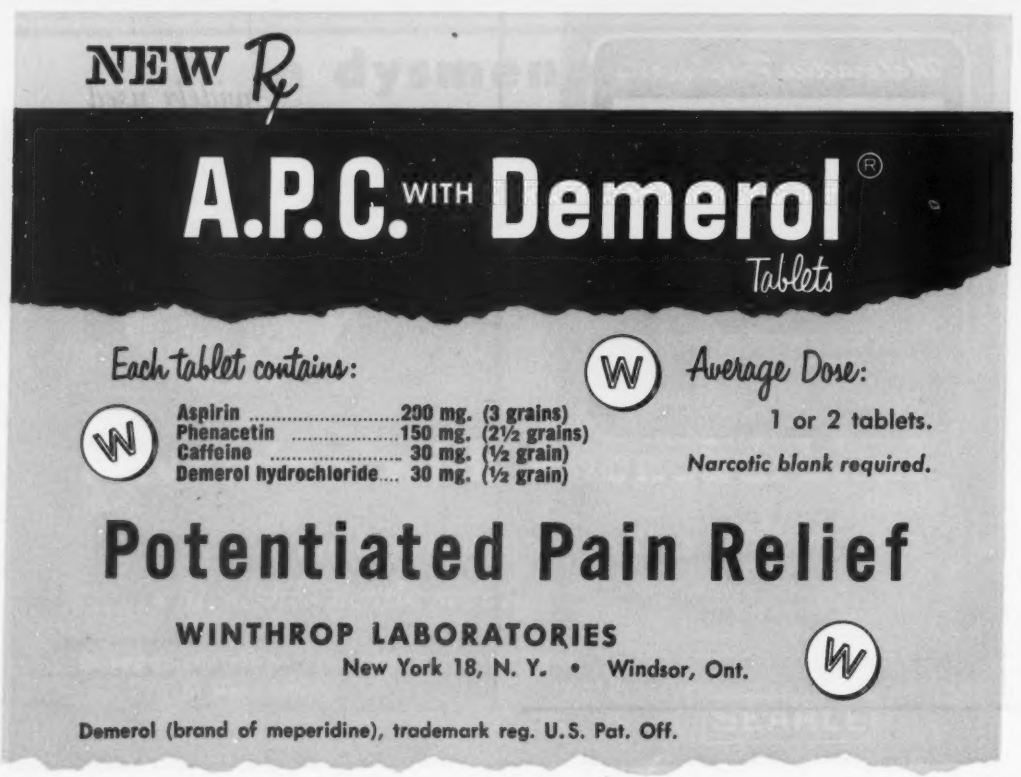
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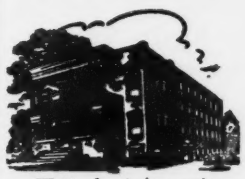

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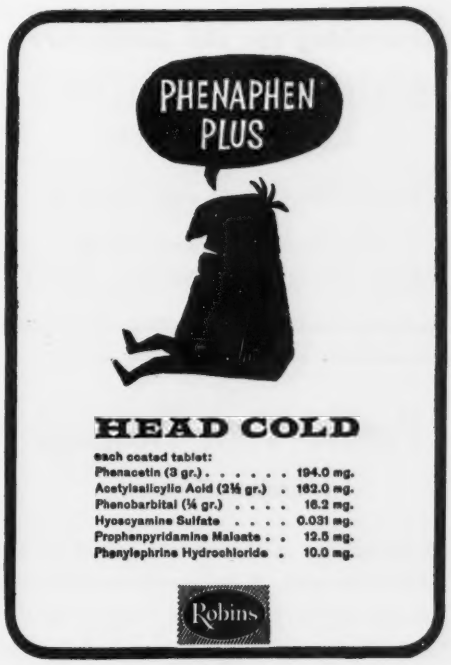

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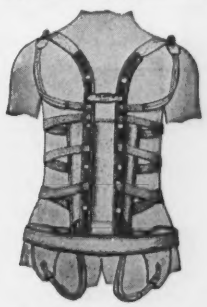

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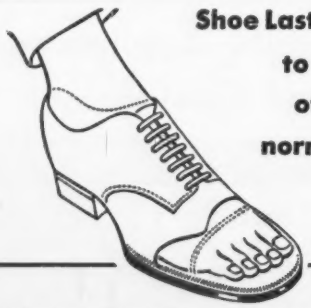

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April 8, 9, 10, 11 & 12

Guest Instructors:

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DAVID D. DONALDSON, M.D., Massachusetts Eye & Ear Infirmary, Harvard University, Boston

JOSEPH S. HAAS, M.D., Eye & Ear Infirmary, University of Illinois, Chicago

HUGH L. ORMSBY, M.D., University of Toronto, Toronto, Ont., Can.

LYLE M. SELLERS, M.D., Southwestern Medical School, University of Texas, Dallas

MAURICE F. SNITMAN, M.D., University of Illinois, Chicago

HANS VON LEDEN, M.D., Northwestern University & Cook County Graduate School, Chicago

LORENZ E. ZIMMERMAN, M.D., George Washington University & Armed Forces Institute of Pathology, Washington, D. C.

BYRON J. ASHLEY, M.D., Topeka

GEORGE F. GSELL, M.D., Wichita

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April 15, 16 and 17

Guest Instructors:

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CHARLES L. BURSTEIN, M.D., New York University Post-Graduate Medical School, New York City

FORREST E. LEFFINGWELL, M.D., College of Medical Evangelists, Los Angeles

DAVID M. LITTLE, JR., M.D., Hartford Hospital, Hartford, Conn.

WILLIAM O. MCQUISTON, M.D., Northwestern University, Chicago

WILLIAM W. MUSHIN, M.D., University of Wales, Cardiff

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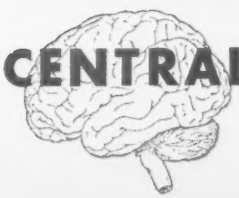

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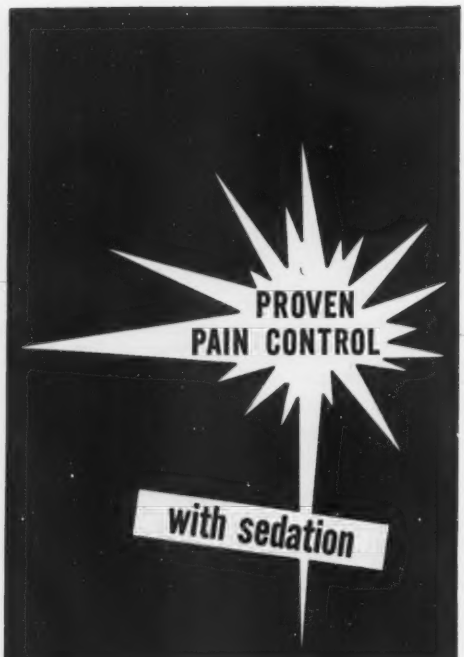

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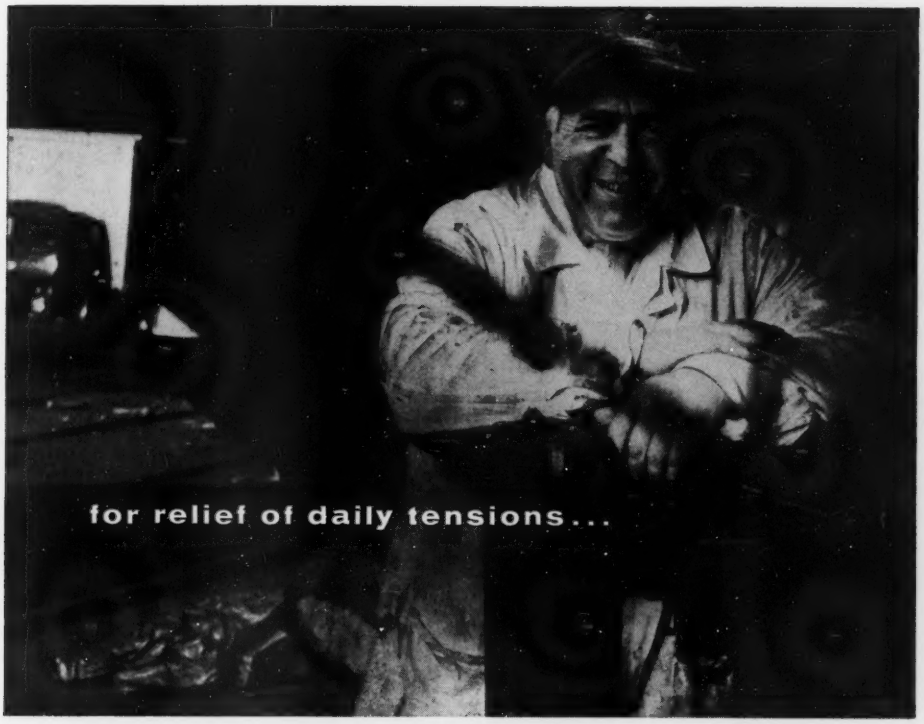

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*Ferguson, J. T.: J. Am. Geriatrics Soc. *4*:1080, 1956.

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